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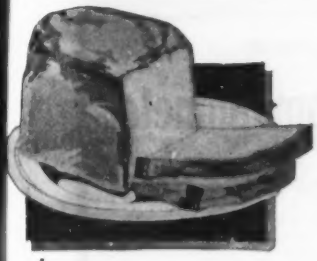

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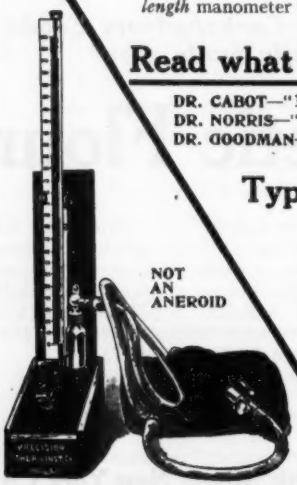

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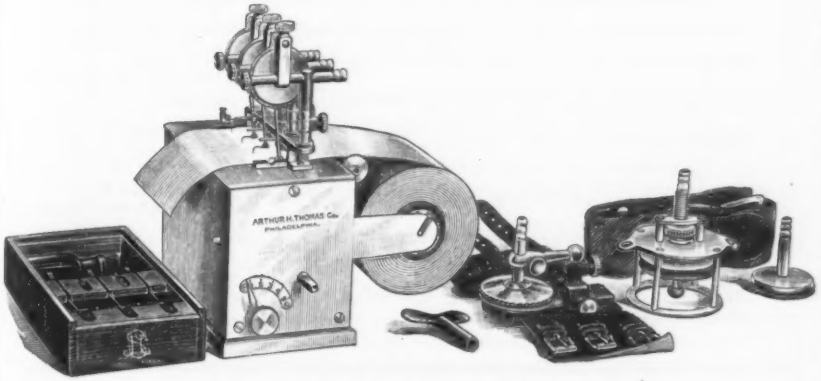

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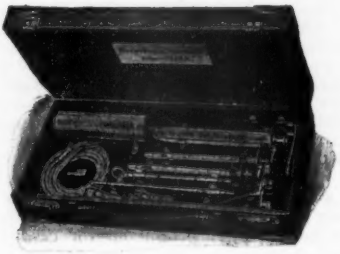

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*Bloom, New Orleans Medical and Surg. Journal, Vol. 70, No. 3, Sept. 1917, page 282.

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ORIGINAL ARTICLES

CLINICAL STUDIES IN CUTANEOUS ASPECTS OF TUBERCULOSIS.

II. THE DIAGNOSTIC AND CLINICAL RELATIONS OF CERTAIN TUBERCULIDS.

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The tuberculid is a cutaneous lesion of exceptional interest to the pathologist, the internist and the general diagnostician. The term was devised by Darier to describe a group of lesions associated with tuberculosis of the viscera, which, while accompaniments of this disease clinically, did not exhibit necessarily the characteristic pathological anatomy of tuberculosis in other structures. Thus, for example, lupus vulgaris is a true tuberculosis of the skin, with the histological architecture associated with the disease in other parts of the body. The papulonecrotic tuberculid, on the other hand, is a localized non-specific type of inflammatory reaction, the individual lesions being papules occurring by preference upon the extremities, each distinguished by a central necrotic plug, which, on separation, permits the healing of the lesion with the formation of a punctate, atrophic scar. Upon the etiology of tuberculids a large amount of clinical and experimental work has been done. The relative degrees of association of the various types with tuberculosis have been widely studied. Lichen scrofulosorum, a grouped, follicular, papular eruption, has been clinically and experimentally demonstrated to be a tuberculid. The papulonecrotic tuberculid, another type of cutaneous lesion, is now generally accepted as of

tuberculous origin, so that its use as a diagnostic criterion in the identification of tuberculous lesions, frank or occult, is justified by a large body of clinical and experimental evidence. Two types of papulo-necrotic lesions with distinguishing characteristics are given separate names in the majority of dermatologic texts. These are acnitis, the papulonecrotic tuberculid of the face, first clinically defined by Barthelemy, and folliclis, the papulonecrotic tuberculid of the extremities. Of the two, the former is stated by Jadassohn to have the more distinctively tuberculoid histopathological structure. A third type of tuberculid, one degree removed, so to speak, from final demonstration as a manifestation of tuberculosis in the skin, is the so-called erythema induratum of Bazin, a plague-like lesion prone to ulceration, most often found upon the lower extremities, especially the calf of the leg. The tuberculous character of this lesion, in spite of its inflammatory architecture, is now practically conceded, especially as a result of the recent rapid advances in methods of demonstrating the tubercle bacillus by animal inoculation, antiformin digestion, etc. It also is a lesion of marked diagnostic value in the recognition of obscure tuberculosis. A number of other lesions for various reasons are now held to be tuberculids, among which might be mentioned acne scrofulosorum, pityriasis rubra pilaris, certain exfoliative erythrodermias, acne necrotica, acne cachecticorum, lupus pernio and the sarcoids. The possible tuberculous relations of lupus erythematosus and of purpura, erythema multiforme and erythema nodosum are also subjects of recent and active discussion. The material of the Mayo Clinic seems to be exceptionally rich in tuberculids, and this has afforded a number of opportunities to study the clinical and diagnostic relations of those types now accepted as on a definitely tuberculous status—the papulonecrotic tuberculid and erythema induratum. I have, moreover, discussed 8 of the cases in the present series of 30 from the standpoint of the relation of erythema nodosum to tuberculosis.*

The crux of the discussion of tuberculids among dermatologists and immunologists has centered about their pathogenesis. This point was admirably brought out in Jadassohn's masterly review of the subject just before the War. It was also dealt with in a symposium before the meeting of the Dermatological Section of the American Medical Association (1918), the discussions to appear in the *Journal of Cutaneous Diseases* during the year. The problem of investigators has been to explain how a lesion, which in pathological architecture is not tuberculous, can present such an unvarying association with a tuberculous focus as that found in the papulonecrotic and erythema induratum types of tuberculids. The theories on which work was at first conducted followed the familiar toxic lines and ascribed the cutaneous lesions to tuberculo-

* Study I, "Tuberculous" purpura, erythema multiforme and erythema nodosum.

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toxins elaborated at a distant focus. The development of experimental methods has, as already intimated, relegated this theory increasingly to the background and brought forward more and more convincing evidence that the tubercle bacillus itself, probably hematogenously distributed, is responsible for the individual lesions of a tuberculid. While organisms are exceedingly difficult to demonstrate in these tissues, positive results are claimed, and the percentage of successful animal inoculations is rising above the margin of experimental error for this mode of establishing tuberculosis. But the demonstration that the tubercle bacillus, whether in viru-

FIG. 1 (191446).—Acnitis, the papulonecrotic tuberculid of the face. Patient had had tuberculous peritonitis. Note the central necrotic plugs and the uniformity in size and age of the lesions. The crop appeared following quinsy, was treated as acne vulgaris and was ascribed by the patient to nux vomica.

lent or attenuated form, is responsible for the lesion is not adequate to explain why in one case hematogenously distributed bacilli gave rise to tubercles and epithelioid changes and in others to merely non-specific inflammatory reactions with necrosis or to fibroid changes of a quasi-neoplastic instead of granulomatous character. In animal experimental work it has been shown that the tubercle bacillus can persist as an embolic invader in veins without setting up more than trivial changes (Liebermeister). Through the work of Saeves in trichophytoses a similar condition of insusceptibility of tissues has been recognized in these diseases. One explanation, that of a difference in the virulence of the invading organism, has had

numerous proponents. It has, however, gradually given place to an explanation based on the different reactivity of different persons and even of different tissues to the organism. In other words, cutaneous allergy or hypersensitiveness has been invoked to explain why one person develops lupus vulgaris, another a papulonecrotic tuberculid, another lichen scrofulosorum and still another, perhaps, a sarcoid. The importance of the allergic factor was effectively demonstrated in the experimental work of Rist and Rolland, and there can be little doubt that while its significance may be overestimated by some investigators, it is one of the best available explanations of the phenomena. For a fuller consideration of the experimental work underlying this theory, reference should be had to the studies of Gougerot, Rist and Rolland and Zieler.

Thus far the principal emphasis has been placed on tuberculin and tuberculo-toxins themselves as the agents that sensitize the tissues to the hematogenously distributed bacilli. Ingenious explanations have been devised to account for the observed failure of certain persons with tuberculids to react to tuberculin in the von Pirquet or intradermal tests. These follow the immunological conceptions applied in explaining the failure of extreme stages of tuberculosis to react to tuberculin. Thus far, however, little account has been taken of the possibility that sensitizing agents other than tuberculin may be responsible for a part of the allergy which makes a tuberculid possible, and that the person who does not react to tuberculin fails to do so because he does not owe his sensitiveness to tuberculin but to some other toxic substance or bacterial product. This point will be raised again in pointing out the association of tuberculids with pyogenic foci of infection, as evidenced in this series. The mechanism of the allergic reaction which results in the formation of the papulonecrotic tuberculid is, roughly, as follows:

Bacilli are carried by the blood stream to a hypersensitive skin and deposited at points where the circulation best favors the lodgment of an embolus—namely, in the extremities. At once a local anaphylactic reaction is set up, an inflammatory papule forms and at the point where the reaction is most intense disintegration of the tissues occurs with central necrosis. In the reaction the organisms which precipitated it are largely destroyed, which accounts for the excessive rarity of their demonstration. The pathological picture is that of an acute inflammation and is practically identical in the papule of a von Pirquet reaction, the papule of folliclis or acnitis and the lesions of erythema induratum. While a tuberculid may not be tuberculosis cutis histopathologically, it is due to the tubercle bacillus, and as such is evidence of its presence in the body. This, in effect, summarizes the trend of modern opinion. It should not be forgotten that, like all generalizations, this one has its borderline, and that it is possible to demonstrate lesions which clinically are tuberculids yet have the architecture of tuberculosis (Harris's case

of dermatitis nodularis necrotica as illustrated in Pusey's *Principles and Practice of Dermatology*).

Tuberculids of the papulonecrotic and erythema induratum type, when recognized, have a considerable value to general diagnosticians as earmarks of obscure tuberculosis. An understanding of their pathological and clinical background often throws much light on elements in the patient's general condition, which may be ignored or misinterpreted. A preliminary description of the type here considered will be of assistance in a comprehension of these relations.

FIG. 2 (200229).—Acnitis, the papulonecrotic tuberculid of the face in a patient with tuberculous adenitis, showing the involvement of the ear by the tuberculid. The black spot in the helix is an active lesion. "Moth-eaten ear."

It must be borne constantly in mind that the distinction between types of papulonecrotic tuberculids—that is, folliclis—the papulonecrotic tuberculid of the hands, or acnitis, that of the face, is largely for clinical convenience, and that one is not exclusive of the other. All the various forms may be present at the same time in the same person or in succession at different periods of his history. The identification of the elementary lesion of a tuberculid, or in fact of any dermatosis, is the first requisite to a diagnosis. The elementary papulonecrotic lesion is exactly what its name indicates. Whether occurring on the face, the hands, the buttock, the legs, the toes, the ears, it is an inflammatory papule exhibiting, in fully developed form, a central necrotic plug of tissue, usually dark in color. In its earlier stages the papule may vesiculate, later drying enough to show the necrotic plug. The plug may, in the later stages

of the lesion, either suppurate out or be picked out by the patient, leaving a conical depression which heals, producing a punctate atrophic scar. The inflammatory process which produced the papule also gives rise to a ring or collarette of hyperpigmentation about the scar, which persists for periods of months or even years in certain situations, especially on the lower extremities, where stasis accentuates the process. A papulonecrotic lesion may vary in size from a large pinhead in folliclis to a pseudofuruncular lesion several centimeters across in dermatitis nodularis necrotica, but if careful examination is made the primitive or essential lesions can usually be found.

FIG. 3 (226884).—Various types of folliclis, the papulonecrotic tuberculid of the hands. An active lesion on the fourth finger of the left hand. Note the typical crater left on removal of the necrotic plug. Patient with tuberculous adenitis.

Failure to recognize papulonecrotic lesions or their scars is quite as often due to faulty methods of examination as to unfamiliarity with the lesion. The localizations and sites of predilection of the lesions are often not inspected by the internist, who is interested in percussing the chest or palpating the abdomen. Instead of making a purely objective examination of the entire body, the busy diagnostician, guided by the history, is likely to overlook the moth-eaten ear of acnitis unless he is expecting gouty tophi. In the same way the backs of the terminal phalanges and the tips of the fingers, the favorite localization for the form of papulonecrotic tuberculid known as folliclis, are seldom the subjects of painstaking inspection by general diagnosticians. Punctate atrophic scars about the

elbows and the extensor surfaces of the forearms are attributed to furuncles and trauma instead of to the tuberculid responsible for them. A poor light, as well as cursory inspection, is responsible for many misconceptions of these lesions. Surprising and entirely unwarrantable operative interference may be practiced upon tuberculids of the leg through insufficient observation or faulty interpretation. Incisions for drainage, excisions with suture, skin grafts and transplants, excisions for diagnosis, with a report of "fibroma," "inflammatory tissue," etc., are frequent. The exquisite tenderness of many of the larger leg lesions combined with central softening is misinterpreted as osteomyelitis or furunculosis and subjected to operative trauma.

FIG. 4 (212370).—Folliclis in a patient with erythema induratum. Note the various stages—a fresh papule on the patient's right little finger, vesicle formation and beginning necrosis on the left little finger, active lesions with central necrosis on the right index and middle finger, scars on the left index and middle fingers.

Erythema induratum is in a sense only an exaggeration of the papulonecrotic lesion. In fact, the larger lesions often seem to be produced by a confluence of smaller nodes. The typical lesion is an erythematous to violaceous plaque usually several centimeters in diameter, firm, indurated and somewhat tender. By predilection these lesions are said to appear on the posterior aspect of the leg in the region of the calf and ankle, but this localization in my experience is by no means constant. Lesions varying all the way from the small necrotic centered papule, through the breaking down nodule to the typical ulcerating plaque may be found scattered about the lower, and at times even the upper, extremities. In fact, the presence

of papulonecrotic lesions is a material aid in diagnosis of a solitary ulcerative plaque of erythema induratum.

The scars of tuberculids are in many ways quite distinctive. This is especially true if their distribution is limited to one or the other of the sites of predilection. A number of these sites with their characteristic lesions and scars are illustrated in Figs. 1–8, 11, 12, 14, 15, 18 and 20. The scar is never contractile or distorting, and in the peculiar punctate atrophy produced may suggest that of a variola, though it is usually deeper.

SUMMARY OF DIFFERENTIAL DIAGNOSIS.

Papulonecrotic Tuberculid of the Face—Acnitis. This condition is to be distinguished from acne vulgaris by the circumscribed papule with central necrosis as distinguished from a pustule or infected comedo and by the uniformity of the lesions, which tend to appear in crops and hence to be, to a considerable extent, of the same age and size. The moth-eaten ear, due to papulonecrotic lesions in this site, is illustrated in Fig. 2. The absence of comedones and seborrhea and of transition lesions from comedone to pustule is significant. Acute acnitis may strongly suggest variola from which its course distinguishes it.

Papulonecrotic Tuberculid of the Extremities—Folliclis. When limited to the hands and feet, there is practically no other lesion which closely simulates it. In the vesicular stage the marked inflammatory papule which forms the bulk of the individual lesion, and the tendency to become hemorrhagic distinguishes it from the sago-grain vesicle of dysidrosis, pompholyx or "sweat eczema," which moreover does not leave scars. In the case of folliclis the patient describes a highly characteristic sign—a feeling as if a thorn were pressing into the flesh when the papule is pressed upon. Their small size and uniform appearance and a frequent tendency to localize in faceted patches or on the dorsal surface of the phalanges, help to distinguish the scars from those of trauma. In cases with marked vasomotor disturbance the diagnosis of Raynaud's disease may be made through failure to observe the scars or to get a careful history of the course of the lesion. Frost-bite is a more diffuse erythematous lesion. Lupus pernio may temporarily simulate folliclis, but the distinction can be made by a search for the elementary lesion and its evolutionary steps as outlined above. The papulonecrotic tuberculid of the trunk is frequently mistaken for furunculosis and for severe acne vulgaris. Here again the search for the elementary lesion reveals it not as a comedone on a seborrheic base but as a papule in which vesicle formation may occur but is usually abortive and in which pustulation is usually secondary to the formation of the dry, hard, necrotic central plug. The large nodules undergo actual ulceration and heal slowly, suggesting ecthyma and

in the pustular phase, a pustular lues. (The absence of transition stages from comedone to pustule eliminates acne.) On the arms and trunk scratch papules must be distinguished. The scratch papule is a secondary infection of a previously produced excoriation, and uninfected or recent excoriations, dried bloodstreaks, linear abrasions and scars can usually be found. Parasites produce the picture of a scratch dermatitis. The nodular lesions of prurigo and lichen urticatus can be distinguished by the fact that they have no central necroses though they show scratch excoriation. They are

FIG. 5 (228772).—Folliclis localiaing at points of greatest trauma. Patient with tuberculous glands.

also accompanied by other evidences of dermatitis, or by wheals and multiform erythematous lesions. The pruritic nodules of Hodgkin's disease may suggest a tuberculid, but their intensely pruritic character and the multiple evidences of scratching, including the history of violent itching, together with the absence of central necroses, eliminate the tuberculid. The nodules of Hodgkin's disease do not primarily localize on the extremities. I have known a generalized tuberculid to be diagnosed a psoriasis in the presence of marked crusting, the diagnostician forgetting that psoriasis does not produce scars.

Papulonecrotic Tuberculids of General Distribution. These lesions may occur in showers, especially involving the trunk. Their tendency to show a vesicular stage and the necrosis as distinguished from pustulation helps to eliminate a pustular syphilide. The diagnosis of this type of lesion may offer great difficulties, and not infrequently the conclusion must depend upon collateral evidence of the presence of tuberculosis and the absence of syphilis and upon recurrence and chronicity. One such case in my series yielded a positive Wassermann reaction on several occasions, and only the recurrence of the lesions through a period of years and the final

FIG. 6 (230740).—Facetted, grouped scars of folliclis, index, middle (tip) and fourth fingers. Vasomotor abnormalities, tuberculous adenitis.

occurrence of typical necrotic papules made the differentiation possible. The scars of a widely distributed tuberculid may suggest those of a pustular syphilid so strongly that serious mistakes may be made. In one such case a positive Wassermann and a mass of glands which cleared under arsphenamin seemed to establish a diagnosis which was reversed by later findings.

There is a distinct tendency for papulonecrotic tuberculids to occur at points of trauma. This fact has, in my experience, led to confusion with epidermolysis bullosa hereditaria, especially when lesions were localized on the elbows. One distinctive site of lesions in epidermolysis bullosa hereditaria, over the thyroid cartilage of

the larynx from collar trauma, I have never known to be the site of tuberculids not involving the face. Moreover, the bullous phase of epidermolysis is much more marked than the vesicular phase of tuberculids, which is often abortive. Nevertheless, the scarring produced by the two conditions may have many points of similarity (Fig. 6).

Erythema Induratum. This condition seldom occurs alone. It usually is associated with papulonecrotic lesions that may group to form larger plaques. The differentiation from nodular lues depends first upon the tendency of the lesions to symmetrical dis-

FIG. 7 (186129).—Scars of folliclis, dorsal surface of fingers. Two involuting lesions on index and middle fingers. Positive Wassermann but no clinical evidence of syphilis.

tribution on both extremities, and second, upon the multiplicity of the lesions and their lack of configuration, that is, their irregular shape and arrangement as distinguished from the grouping into typical arciform or polycyclic arrangements observed in lues. The scars exhibit the same peculiarities (Fig. 7). From gumma of the pretibial region, the solitary character of the gumma and the preference of erythema induratum for the posterior surface distinguish it. It should be remembered, however, that gummas may also be symmetrical and multiple. Multiple infarctions in the skin or anemic ulcers are usually only associated with high degrees of thrombotic occlusion of the vein, which can be seen and palpated

and with suggilation and hemorrhage into the skin and even multiple areas of gangrene. Erythema nodosum is usually distinguished from erythema induratum by the tendency of the latter to ulcerate, and to occur by preference on the posterior surface. As a matter of fact, all stages in the transition from erythema nodosum to erythema induratum both as regards morphology and localization, may be seen in subjects with a tuberculous background, so that some of the distinctions are artificial. Streptococcal or diphtheroid erythema nodosum of the Rosenow type, however, does not ulcerate and the process is, in general, more acute, the nodes more brawny and edematous, and the hemorrhagic and ecchymotic changes and edema more marked than in the tuberculous type. A resumé of this aspect of the problem may be found in the discussion of tuberculous erythema nodosum in the first study of this series.

FIG. 8 (171947).—Papulonecrotic lesions on the foot and ankle of a patient who also had erythema induratum. Note the nodules that have not yet undergone central necrosis, as well as the necrotic lesions with black central plugs.

Ulcerative erythema induratum is to be differentiated from noduloulcerative syphilids again by its tendency to symmetry, which, however, is no more invariable than is asymmetry in lues. The luetic ulcer has a configuration which can be recognized by practice as segmental or arciform. The erythema induratum ulcer is irregular and nondescript. Instead of a sharp margin closely bordered by normal skin, the erythema induratum ulcer is usually undermined, has a thin grumous or hemorrhagic discharge, and is surrounded by bluish scrofulodermatous sodden tissue. There is

usually no definite gummatous slough as in lues. The concomitant occurrence of papulonecrotic lesions and nodules greatly assists in the recognition of erythema induratum. The typical chronic varicose ulcer is easily differentiated by its rigid scar tissue border, its flat open floor of anemic granulations and the usual regularity of its margin. Epithelioma is usually unilateral and has a highly characteristic nodular and rolled pearly margin.

A word of warning should be given as to the use of arsphenamin in an attempt to make a differentiation between a tuberculid and a syphilitic lesion by therapeutic test. Tuberculids, as will be seen in a subsequent paper, respond rapidly to this form of medication, so that a false therapeutic effect is produced which may subject the patient to prolonged treatment for a non-existent lues.

CLINICAL RESUMÉ OF THIRTY CASES OF PAPULONECROTIC TUBERCULID AND ERYTHEMA INDURATUM.

The series of cases collected by the writer during the past two years illustrates in a convincing way the association of these conditions with tuberculosis. Of the thirty cases 80 per cent. were women. This preponderance of women over men has been recognized by others. In a series of 100 cases of tuberculous adenitis reviewed in connection with this study a similar proportion of 64 per cent. women and 36 per cent. men was observed. The youngest patient was ten years of age, the oldest fifty-one. Of 13 cases in which data were available the onset of the tuberculid had been in the second or third decade of life in 12, corresponding in this particular to the period of greatest incidence of signs of systemic tuberculosis.

Eighty-three per cent. of the 30 patients bore evidence of past or present lesions of the papulonecrotic type. Three had lesions on the face (acnitis), 12 had lesions or scars on the hands (folliclis), 15 had papulonecrotic lesions on the legs and 9 had them on the trunk. Only 2 patients presented an erythema induratum uncomplicated by another tuberculid. One of these had apparently a tuberculosis verrucosa cutis and the other had undoubted tuberculous adenitis. It is apparent that in its association with other more definitely proved tuberculids in this series, erythema induratum establishes, still further, its claim to a tuberculous origin.

RELATION OF THE CUTANEOUS LESIONS TO SYSTEMIC TUBERCULOSIS.

History of Tuberculosis in the Family or Patient. A definite history of tuberculosis in the family, sufficiently direct to bring the patient into contact with it, was given by one-fourth of the cases (23 per cent.). Somewhat more than one-third of the patients had been diagnosed as tuberculous previous to their examination in the

clinic. The diagnosis was usually based upon adenopathy rather than on pulmonary or other signs.

The Objective Manifestations of Tuberculosis. It is to be understood that tuberculids as signs of tuberculosis are excluded. Fifty-seven per cent., or more than half of the entire series, showed incontrovertible systemic objective signs of tuberculosis, usually in such numbers that had any one sign been insufficient the others would have confirmed the diagnosis.

Thirteen per cent. of the cases were rated as disputable, and 30 per cent. presented no definite signs. Table I, summarizing the disputable and occult cases, is here appended.

TABLE I.

DOUBTFUL CASES.

Case A202732—Erythema nodosum; loss of weight; doubtful lung lesion as revealed by *x*-ray and physical examination.

Case A212370—Tenosynovitis, tuberculous(?) (folliclis, erythema induratum).

Case A188556—Erythema nodosum and erythema multiforme. Enlarged right cervical glands; temperature and lung signs.

Case A224920—Family riddled by tuberculosis; patient underweight; asthenic; well-defined signs in right apex (folliclis, fingers and toes).

OCCULT CASES.

Case A39183— Obscure anemia; inflammatory changes in abdomen; positive and negative Wassermann at various times, menorrhagia; headaches; generalized papulonecrotic tuberculid.

Case A197825—Florid, obese girl; no signs of tuberculosis; erythema induratum.

Case A221958—Positive Wassermann without history or evidence of syphilis; lupus erythematosus of the face; folliclis, scars on fingers.

Case A218528—Anemia, persistent; marked loss of weight; erythema induratum and papulonecrotic tuberculid of the legs.

Case A201284—Anemia, pernicious (?); extreme hyperpigmentation; cachexia; tuberculid of the legs; lupus erythematosus; adrenal tuberculosis(?).

Case A171947—General examination negative; obese, well nourished woman; extensive papulonecrotic tuberculid of the legs with erythema induratum.

Case A63167—Iritis in childhood; tuberculosis of the knee (?); three weak positive Wassermanns, without evidence of lues; alveolar abscess, otherwise negative; papulonecrotic tuberculid of legs and elbows; erythema induratum.

Case A186129—Repeated positive Wassermann; exposure, but no evidence of lues; folliclis of hands; scars of papulonecrotic tuberculid of the body.

Case A233765—Obese girl, no signs of tuberculosis, but von Pirquet strongly positive; erythema nodosum and induratum; legs and arms involved, with purpuric lesions.

The occult cases form a group of special interest. The mere fact that a gross focus of tuberculosis cannot be demonstrated is of course not an evidence that such a focus may not exist, in the retroperitoneal glands, for example, or in the uterine adnexa.[6]

Two of our patients gave histories suggestive of such a focus but in the absence of operative exploration the focus could not be demonstrated. Four of the 9 occult cases were in florid, rather obese persons, of a type recognized as predisposed to some extent to tuberculous infection.

One-third of 27 cases in which radiograms of the thorax were made showed evidence of pulmonary tuberculosis. The involvements were largely apical, with calcification and signs of healing in several. The importance of a tuberculid as a diagnostic lead for the internist can be appreciated from such a finding. Four cases showed doubtful *x*-ray signs of little independent value. One-third of the cases likewise presented physical signs suggestive of pulmonary tuberculosis. Both physical and *x*-ray findings were present in 5 (17 per cent.) of 29 cases.

More than two-thirds of the patients had a visible and palpable lymph-adenitis, making glandular involvement the commonest form of tuberculosis associated with these tuberculids. In 38 per cent. the adenitis was marked. This very evident association of tuberculids with glandular tuberculosis forms a theoretical basis for explaining their presence in occult cases without visible manifestations. Moreover, the association of tuberculids with a form of tuberculosis that, in a broad way, indicates a high individual resistance to the bacillus is of interesting prognostic significance, and suggests that a tuberculid, among other signs, may be in a way accepted as evidence of a benign course of the disease. This point is of interest in connection with the older conceptions of the extreme gravity of the papulonecrotic tuberculid in infancy. A recent study by Hempelmann has brought forward evidence to show that even in infancy the association with lymphatic tuberculosis (tracheobronchial node involvement) can be recognized, and that the prognosis in cases with tuberculids is no graver than in those without.

Among other forms of tuberculosis with which tuberculids in this group were associated the following should be mentioned: sacro-iliac abscess, tuberculous peritonitis, renal tuberculosis (bacilli demonstrated) and tuberculosis verrucosa cutis one case each, tuberculous keratitis 3 cases. In one patient the tuberculosis verrucosa cutis occurred on the right leg, the erythema induratum on the calf of the left.

FIG. 9 (171947).—Serpiginous ulcers produced by the confluence of solitary nodules and plaques. Scar of unwarranted surgical interference on the left leg.

Prevalence of Tuberculids in Connection with Tuberculous Glands. In endeavoring to ascertain the prevalence of tuberculids in cases of tuberculous adenitis, as observed by internists in the material of a large clinic, 100 cases of tuberculous adenitis were reviewed for evidence that any cutaneous lesion had been observed. In this series 10 per cent. were described as having lesions which could be inferred to be tuberculids. The proportion of men to women among those having cutaneous lesions was as 1 to 10, which is not far removed

from the percentage observed in the series of tuberculids under discussion. There can be little doubt that a number of the less obvious tuberculids were overlooked and that 10 per cent is too small a figure for the incidence of these lesions in glandular tuberculosis.

A careful comparative study of the cutaneous lesions and the types of tuberculous systemic involvement failed to reveal any constant relation between the tuberculous focus and the type of tuberculid. On the other hand, a definite relation between vasomotor and stasis phenomena and the distribution of the tuberculid, was apparent. There was also evidence to show that the more extensive tuber-

FIG. 10 (219380).—Solitary gummatous ulcer with edema and infiltration of the surrounding tissue, to show the differential points.

culids in a rough way were associated with what seemed the more extensive and serious types of systemic tuberculous involvement. Seven of the 9 cases presenting extensive tuberculids involving trunk and extremities also presented the most serious forms of tuberculous involvement in the series.

RELATION OF VASOMOTOR PHENOMENA AND VASCULAR STASIS TO THE DISTRIBUTION OF TUBERCULIDS.

It has long been recognized that a tuberculid tends to appear upon the extremities, and especially to appear in those patients in

whom the peripheral circulation is feeble or obstructed. Data on the collateral local vascular findings were collected on 28 cases in this series. Of these one-half (50 per cent.) showed abnormalities of the vascular supply in the form of cyanosis and vasomotor anomalies of the extremities, and swollen hands, legs or feet. Every "stasis leg," that is one with a tendency to passive congestion from defective venous return, had erythema induratum. Five of 7 with blue hands had folliclis. The possession of a leg with a tendency to vascular stasis thus predisposes, to the extent of nearly 100 per cent., to the type of tuberculid known as erythema induratum.

FIG. 11

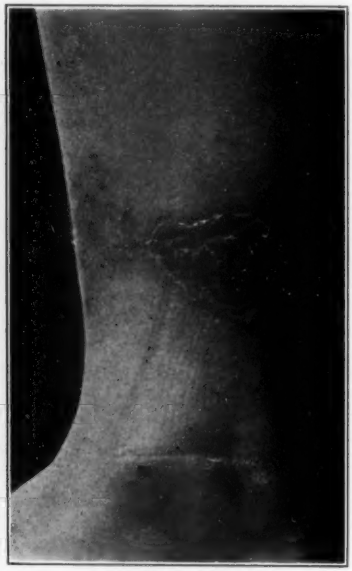

FIG. 11a

FIG. 11 and 11a (218528).—Erythema induratum with papulonecrotic lesions on the legs of a patient of the "occult" type.

In the same way, the possession of cold, clammy, mottled hands predisposes to the extent of more than 70 per cent., to the development of folliclis. It was a matter of note that all the patients who, at the onset of their cutaneous lesions, had been overweight showed the severest part of their manifestations in the lower extremities; a fact which accords well with the vascular stasis usually present in such legs. Obese persons, therefore, seem to be predisposed to the erythema induratum type of tuberculid, and the thin and neurotic with marked vasomotor imbalance, to folliclis. Only 2 of 7 obese patients had folliclis, and one of these was a child with a generalized tuberculid.

Summarizing the series as a whole from the standpoint of localization of lesions, more than half (57 per cent.) of the patients had lesions on the upper extremities, but almost three-fourths (74 per cent.) had them on the lower extremities, showing the distinct predilection for parts of slower circulation. Ninety-six per cent. of the patients, or practically all, had lesions on either upper or lower extremities. Twenty-three per cent. had lesions on the upper extremities and not on the lower; 43 per cent. on the lower and not on the upper, so that the odds are 2 to 1 in favor of the lower extremity as a site of involvement. One-third had involvement of both extremities, one-third showed involvement of the trunk, and one-fifth of the face. It is of interest to note that 65 per cent. of those in whom the face was involved had lesions on the ears, and that the ear was the seat of lesions in 13 per cent. of the whole series (Fig. 2).

The importance of the circulatory factor in the distribution of tuberculids is one of the strongest arguments for the bacillemic as opposed to the toxemic origin of the process. The presumption is that at points where the circulatory stream is moving most slowly the maximum opportunity for the deposit of organisms will present itself, and that lesions will tend to appear, as they do, in areas where one factor or another acts to delay the movement of the blood.

MISCELLANEOUS FINDINGS ON EXAMINATION.

In the study of this series of cases a number of interesting miscellaneous findings developed. The recognition of concomitant tuberculosis in cases exhibiting a tuberculid is, on the whole, a matter of identifying signs by objective examination rather than of eliciting symptoms. Six of the patients had a temperature of 99° or over at the time of examination, although temperature is a much more important factor at onset, especially in those cases which begin as erythema multiforme or erythema nodosum. Of a series of 7 such acute cases, 5 showed temperatures varying from 99° to 103°. Cough had been a well-defined symptom in only 7 of 25 cases, or less than one-third; night-sweats occurred in none, sputum in only 2, both negative for bacilli. On the other hand, amenorrhea was a definite symptom in 43 per cent. of the cases, and in some was coincident with the greatest activity of the tuberculid. Losses of weight, varying from 2 to 45 pounds occurred in 40 per cent., more than half losing less than 10 pounds.

The periodicity of tuberculids and their tendency to exacerbation in spring and fall, which is an important factor in treatment and an aid to diagnosis, were apparent in nearly half of 20 cases in which data were obtained. More than three times as many recurred in spring as in fall, and one-fourth of the patients had lesions continuously.

A little less than half the cases presented secondary anemias with a hemoglobin below 70 per cent. (Dare). In one-fourth of the cases it was below 53 per cent., the lowest being 30 per cent. In the latter case a possibility of a pernicious anemia was entertained. From two of the anemias the influence of syphilis could not be

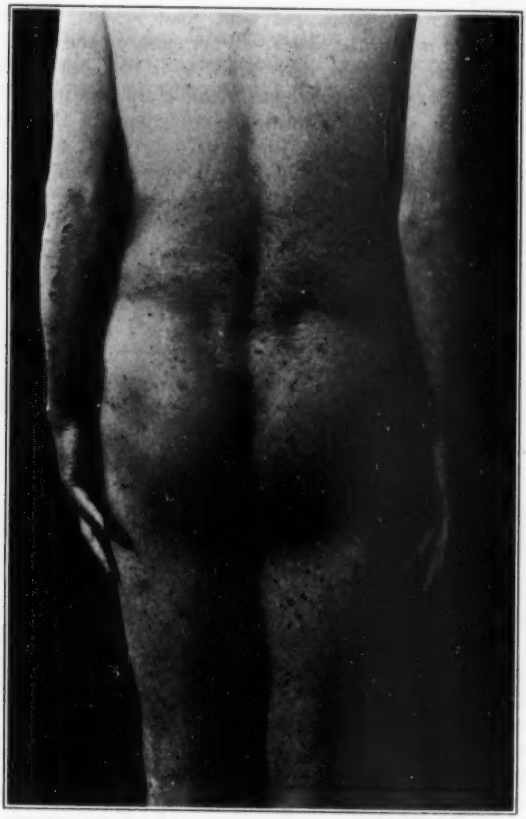

FIG. 12 (226884).—Scars and pigmented residue of acne scrofulosorum, the papulonecrotic tuberculid of the trunk in a patient with tuberculous adenitis. Note lesions on the extensor surfaces of the forearms also. This patient also had lesions of folliclis on the fingers.

eliminated. Accompanying the anemia was a tendency to leukopenia. Even in the acute cases the patients did not, while febrile, exhibit any tendency to leukocytosis. Thirteen of 25 patients had counts below 6600, 8 below 5800. Only 3 exceeded 10,000. No differential counts were taken. On the score of blood-pressure 35 per cent. were below 120, the lowest 98; 40 per cent. were normal,

and 25 per cent. exceeded 135 systolic, the highest being 142. The higher pressures were all in persons under 31. The diastolic and pulse-pressures exhibited no distinctive variations. Observations on the Wassermann test in the tuberculids will be included in the discussion of allergic manifestations.

It is apparent from this review that the clinical accompaniments of a tuberculid tend to be those of a low-grade tuberculous infection. A moderate secondary anemia and leukopenia with occasionally an afternoon temperature, most likely to appear during exacerbations; moderate loss in weight; occasionally cough associated with a lighting up of the acute process, and signs of a definite but not fulminating process in the lungs or glands make up the average clinical picture in a large percentage of the cases. The florid type of case must constantly be borne in mind in dealing with tuberculids, and mere robustness, weight and color must not be accepted as invalidating a diagnosis based on the tuberculid.

THE TUBERCULID IN DIAGNOSIS.

While some caution must be exercised in inferring the diagnostic career of a case from the patient's history or examination, such a study of our series of cases suggested several points of interest. In only 5 of the 30 cases referred for diagnosis to our department had a correct diagnosis been made, and tuberculosis on the score of their cutaneous manifestations had not been suspected. In 2 of the 5 cases the diagnosis might have been made by the internist, but was later made by a dermatologist before the patient was seen by us. In more than one-third of the cases the tuberculid had either been overlooked or ignored as insignificant. This was especially true of acnitis on the face and of folliclis on the fingers. In another third of the cases the cutaneous lesion had been misdiagnosed, to judge from the history or treatment. Six of the 9 cases in this second group had been interpreted as syphilitic, 3 because of the finding of a positive Wassermann, a point to be discussed in connection with allergy. Two were interpreted as luetic because of the history of what was probably a general or extensive shower of tuberculid lesions, of which the scars were present. Another point which seemed to suggest lues was the history of arthritis, myalgia and indefinite pains with mild anemia often given by these patients. Six cases, or one-fifth of the series, had sustained probably needless operative procedures in the effort to make a pathologic diagnosis from the lesions, or for excision, curettage or drainage. The vasomotor and stasis factors had led to a diagnosis of Raynaud's disease in one case, and varicose ulcer in another. One, because of lesions on the elbows, in spite of obvious scars, sustained a diagnosis of psoriasis.

It is apparent that unfamiliarity with the lesions and failure to

observe, whether due to poor light or other cause, together with the tendency to interpret a tuberculid as syphilis, account for four-fifths of the diagnostic errors. For the former difficulty the remedy is obvious. For the latter it should be recalled that not all skin lesions that occur in the presence of a positive Wassermann reaction are syphilitic, and that the recognition of syphilis does not remove

FIG. 13 (234128).—Characteristic scarring and active lesions of the papulonecrotic tuberculid on the elbows of a patient with tuberculous adenitis.

the obligation to ferret out an associated tuberculosis, particularly when the cutaneous evidence points toward it. The occurrence of false positive Wassermann reactions from cholesterinized antigens in the presence of tuberculosis and the absence of syphilis is also being gradually established. The occurrence of tuberculids in crops, their wide distribution upon the face, trunk and extremities, and the frequently associated myalgias and arthralgias are the points in the

history which seem to suggest lues and septic foci rather than obscure tuberculosis to the casual mind. The usefulness of the tuberculid in determining the character of an adenopathy was attested in several cases in which internists had estimated the diagnostic possibilities of cases at 30 to 70 per cent. in favor of Hodgkin's disease, and asked for excisions for diagnosis before seeing the report of the dermatologist.

THE COLLATERAL INFECTION FACTOR: ANAMNESIS.

One of the most interesting relations brought out by this clinical study of the tuberculids was that of collateral types of infection shown in the history and in the examination. In the histories of these patients, five syndromes stand out with overwhelming prominence. These are tonsillitis and "rheumatism;" and pneumonia, grippe and pleurisy. The extraordinary prevalence of these two types of infections, representing the focal infections traceable to tonsillar and alveolar pathology and the respiratory group may be seen in Table II. Since the records in these cases were taken by men who had no conception of a possible relationship between the dermatosis and the systemic condition, they are probably quite unprejudiced.

TABLE II.

HISTORY OF ACUTE INFECTIONS.

Case.	Tonsillitis.	Rheumatism.	Pneumonia.	Grippe.	Pleurisy.
200229	X	..	..	X	
202732	..	..	..	X	
186129	X	X			
200833	X	..	X	X	X
212370	X	X			
194150	X	X	X	X	
157847	..	..	..	X	
169350	X	X	..	X	X
174923	..	X	X		
39183	..	..	X		
188556	..	..	..	X	
197425	..	X	X	X	
221958	..	..	..	X	
154673	..	..	..	X	
228021	X				
49238	..	X			
224920	X				
228772	X	..	..	X	X
218528	..	..	..	X	X
161592	X	..	X		
191446	X	X			
201284	..	..	..	X	
171947	..	..	..	X	
63167	..	X	X	..	X
230740	..	X			
226884	..	X	X		
233765	..	X	..	X	
234128	..	X			
Total	11	13	8	15	5
	39%	46%	29%	54%	18%

Summarizing Table II, it appears that of 28 patients, 39 per cent. had had tonsillitis and 46 per cent. had had rheumatism. Twenty-nine per cent. had had pneumonia, 54 per cent. had had grippe, and 18 per cent. had had pleurisy. Nearly 70 per cent. had had tonsillar infections or rheumatism; 62 per cent. had had definite respiratory infections, not including pleurisy.

TABLE III.

APPARENT ETIOLOGIC CONNECTIONS.

Case 186129—Outbreak of general papulonecrotic tuberculid in the spring following a winter of repeated tonsillitis and colds.

Case 169350—Five years of rheumatoid pains. Grippe followed by pleurisy and abdominal symptoms two years previous to examination; loss of weight, then outbreak of a papulonecrotic tuberculid. No improvement from tonsillectomy.

Case 154673—Grippe; while recovering, purpura and a papulonecrotic tuberculid.

Case 188556—"Cold," with temperature, erythema nodosum, marked glandular enlargement on the right side of the neck, signs over right apex.

Case 197425—Pneumonia 1914, "rheumatism" 1914–1917, then grippe and an outbreak of erythema induratum.

Case 212370—Tonsillitis, followed by tuberculid, rheumatism, hydrarthyrosis, tenosynovitis, tonsils removed without benefit, appendectomy no effect, cleared under treatment for the tuberculid. Teeth negative.

Case 191446—Folliclis for many years following tuberculous peritonitis. Quinsy three months previous to examination followed by an abrupt outbreak of acnitis in addition to the folliclis. Alveolar abscess.

Case 230740—Pneumonia 1913, axillary glands then enlarged, removed in 1916, coincidentally with onset of tuberculid.

Case 174925—Pneumonia sixteen years previously, followed by enlarging glands, removed by operation nine years later. Removal of the glands was followed by severe rheumatism, continuous up to present time. Tuberculid appeared one year after operation; glands recurred.

By the term "rheumatic symptoms" in the foregoing discussion is meant the group of myalgias, neuritides, arthralgias, and occasional arthropathies which do not fall definitely into the category of

acute articular infections. So striking has been the association of this nondescript group of symptoms with the tuberculids that it is now our practice in addition to the routine search for a focus of pyogenic infection in tonsils or teeth, to ray the chests of patients who, in association with suspicious eruptions, complain of "rheumatism."

THE COLLATERAL INFECTION FACTOR: FINDINGS.

Examination of the Tonsils. Data on the clinical condition of the tonsils were available in 21 cases of the 30. It is to be regretted that

FIG. 14 (228772).—Tuberculid scarring on the elbows.

no pathologic examinations were made in those patients who sustained tonsillectomy while they were under observation. The information derived from clinical examination by an otolaryngologist was briefly as follows:

An exceptional degree of tonsillar infection seemed to prevail in the series as a whole. One-half of the patients were rated as having large and badly infected tonsils. The other half were passable and borderline cases. Practically none were entirely within the limits of normality. On the other hand, curious contradictions seemed to exist in the picture. Almost an inverse ratio appeared to prevail

FIG. 15 (103534).—Scarring about the elbow of a patient with epidermolysis bullosa hereditaria.

between the condition of the tonsil and the severity of the tuberculid. Certainly there was nothing to indicate that the severe tuberculids were directly associated with severe tonsillar infection as seen in purely clinical examination. To confirm this evidence of the absence of direct causal relation between tonsil and tuberculid it appeared moreover, that:

1. The tonsils in patients with tuberculous signs were no worse than in those without. They should have been worse in the latter if they were to play the sole etiologic role.

2. No one tuberculid seemed to bear any special relation to the condition of the tonsils.

3. The tuberculid appeared after tonsillectomy in 3 instances.

4. Tonsillectomy performed in 7 instances failed to prevent or modify the course of the tuberculid.

In the light of these considerations it would appear that there is an indirect relation between infected tonsils and the presence of tuberculids, but no direct relation, both in the history and examination. In other words, the septic tonsil is probably not the tuberculous focus. If it is a factor in the situation, its more probable role is that of a predisposing or contributing factor.

Examination of the Teeth. This very important examination was not begun as a routine, unfortunately, until comparatively late in the series, when in studying the clinical picture, the frequent occurrence of a secondary focus became apparent. The results of an examination of 9 cases by *x*-ray showed alveolar abscesses in 3 and a rarefying osteitis of the alveolar process in one. The presence of definite dental pathology in 45 per cent. of the few patients examined is highly suggestive. It should be emphasized that gross examination of the teeth may afford no clue to the condition beyond the suspicions aroused by dental work which is founded on devitalized teeth. That the alveolar focus is not the leading factor in the production of a tuberculid is again evidenced by the fact that it is not invariably present, and that in two cases in which the teeth were normal to examination and tonsils were out (in one of the two even the appendix was removed) the tuberculid and the accompanying arthritic manifestations, including a tenosynovitis, remained unaltered until the institutions of measures directed against the actual or presumptive tuberculous focus.

It should not be forgotten that the search for a secondary focus in connection with a tuberculid should not terminate with tonsils or teeth. In one of our cases the history and findings suggested an infected gall-bladder as a focus, although the teeth were negative and the tonsils were only moderately involved.

THE POSSIBLE BEARING OF CERTAIN ALLERGIC PHENOMENA ON THE ETIOLOGY OF TUBERCULIDS.

Reference was made in the earlier part of this paper to the growth of a body of clinical and experimental evidence in support of an allergic factor in the etiology of tuberculids. As the prime exciter of the cutaneous allergy theoretically necessary to produce the non-specific types of reaction represented by tuberculids, tuberculotoxins have been accepted by investigators apparently with wholehearted enthusiasm. Undoubtedly their role is an important if not

the major one. This enthusiasm has for the time being excluded from the field of vision other agents besides tuberculotoxins which are able to excite a non-specific type of cutaneous allergy. For some years the cutaneous allergy of late syphilis (Umstimmung), for example, was regarded as highly specific, and the enthusiasm with which luetin was received and used was evidence of this uncritical point of view. It was not until certain observers somewhat more skeptically inclined than the average, such as Boas, began to note the behavior of the skin to controls for luetin, that a field was opened for a non-specific interpretation. Sherrick's observation that the allergy of late lues, as evidenced by reactivity to luetin could be artificially produced by the administration of potassium iodide was a major contribution. In 1916 I argued upon theoretical grounds that the behavior of luetin was not due to the spirochetes which it contained but to an adsorption complex in which agar, the culture medium, probably played a principal role. Acting on the theoretical considerations then presented, I succeeded in showing that agar in proper concentration makes an entirely satisfactory substitute for luetin in the luetin test as applied to late syphilis, and that accordingly the reaction and the allergy on which it depended were alike non-specific. In the course of my study of this phenomenon I was able to demonstrate that an allergy clinically similar to the non-specific allergy of syphilis could be artificially produced by the intradermal injection and lysis of even an autogenous and homologous protein. In this experimental work I employed an emulsion of normal skin, both my own and that of my assistant. As a result apparently of a series of injections of this allergy-producing protein, my assistant and I developed a reactivity to agar which in all respects imitated the allergy of late syphilis. This is essentially an experimental proof of the fact that cutaneous allergy of some types as observed in a disease such as syphilis can be artificially imitated by the intradermal introduction of other proteins than those of the specific organism of the disease. While it is not offered as adequate explanation of the allergic phenomena in tuberculosis as manifested in the development of tuberculids, it is at least suggestive of the idea that proteins other than tuberculo-toxins may be responsible for the allergy that makes tuberculids possible. Such proteins may, in the light of the foregoing clinical observations, be staphylotoxins and streptotoxins, derived from what I have called the secondary focus observed in these cases. It is not impossible that the lysis of such toxins in the body or even of the bacteria themselves in recurrent bacteremias may so sensitize the skin that an embolus of tubercle bacilli will provoke a violent inflammatory reaction of a wholly non-specific character, precisely as agar does in the hypersensitive skin of late syphilis. The allergic specificity of the tuberculin reaction has not as yet been subjected to critical analysis in the light of investigations of the type

detailed above. There are indications that there is a non-specific as well as a specific element in the behavior of tuberculin, not the least of which is Meirowsky's observation, confirmed by Zieler, that the sites of "syphilin" reactions react locally to tuberculin.[7]

The resemblances between the immunologic and allergic phenomena in syphilis and tuberculosis are strengthened by what is still inconclusive but highly suggestive evidence of the lapse in specificity of the Wassermann reaction when tuberculids or tuberculous allergic phenomena are concerned. The present clinical study

FIG. 16 (103534).—Types of scarring on the lower extremities. Epidermolysis bullosa hereditaria—the same patient whose elbows appear in Fig. 15.

and other observations on the behavior of the Wassermann reaction in glandular and occult tuberculosis are gradually accumulating a series of cases in which the presumption against syphilis is so strong that even a positive Wassermann must be guardedly accepted. In this series there were four cases in which positive Wassermanns had been obtained, not once but repeatedly. One of the four patients had three weak positive reactions, on the strength of which she had had intermittent treatment for syphilis for a number of years. In three of the cases treatment seemed to secure a reversal

to negative. On the other hand, in three of the cases absolutely no presumptive evidence of an infection has been obtained. Even the therapeutic effects observed are explainable on other grounds. In this connection I recall several cases of tuberculous glands with positive Wassermann reactions, and a case of tuberculous keratitis without evidence of syphilis which cleared up under salvarsan following a single strong positive Wassermann, only to relapse clinically although the Wassermann remained negative. Had these associations in my experience been unsupported in the literature I should have dismissed them as without significance. Jadassohn,

FIG. 17 (174923).—Scarring of a rather large papulonecrotic tuberculid on the calf of the leg. Note the multiplicity of lesions, lack of configuration, peripheral hyperpigmentation. Patient with tuberculous adenitis and arthritic symptoms.

however, refers to Török's observation of positive Wassermanns in association with tuberculids, usually partial positives with one or two antigens. Ravaut, just before the war, had the same experience with several cases in which syphilis could apparently be excluded. Snow and Cooper, as a result of the study of the Wassermann in an army tuberculosis sanitarium, conclude that partial positives in tuberculosis do occur in the absence of syphilis and that they may be due to the cholesterin in cholesterinized antigens. Petroff regards these observations as fully confirmed. My own clinical observations on this point are recorded without further comment, since it is impossible to generalize on so small a group of

cases. In view of these observations it behooves the clinician to give a second thought to the positive Wassermann in association with a tuberculid before accepting it as evidence of syphilis. The caution with reference to the therapeutic test in this connection (p. 325) should also be recalled.

Certain other evidence of an allergic instability in patients with tuberculids appeared in the course of the salvarsan treatment of the patients, and will be discussed in another paper. Of 18 cases on

FIG. 18 (212370).—Hyperpigmentation and scarring due to papulonecrotic lesions on a stasis leg. Patient also had folliclis on the fingers.

which data are available, 9, or 50 per cent., showed varying degrees of idiosyncrasy to arsphenamin or neoarsphenamin. Four reacted acutely, by nitritoid crises on the table, two of them repeatedly. One had a delayed reaction with a toxic erythema, three had gastro-intestinal reactions repeatedly and one ran temperatures after injections. This percentage of reactivity enormously exceeds the average observed in patients on the dermatologic service and points to a marked intolerance or instability.

The importance of doing tuberculin reactions in all cases was not appreciated until the evidence of allergic peculiarities began to appear. They were, therefore, done in only 6, by the von Pirquet method. Three active cases were positive and 3 less active cases were negative. The results of tuberculin therapy will be summarized in a subsequent paper. No conclusions should be drawn from the results mentioned here.

Allergy and the Interpretation of the Secondary Focus in Tuberculids. It should be understood that no attempt is made to consider either the existence or the importance of a secondary pyogenic focus in cases exhibiting tuberculids, as demonstrated by so small a series as 30 cases. None the less the material studied strongly suggests such a factor. Whether a seemingly pyogenic focal disturbance such as erythema nodosum is a forerunner of tuberculosis as suggested in 1907 by Abt, and as mentioned by Jadassohn in 1915, or merely a follower, remains undecided. It is, of course conceivable on the one hand that a co-existent source of pyogenic infection prepares the soil for tuberculosis much as measles increases the susceptibility to the disease. On the other hand, a tuberculous infection may prepare the soil for the pyogenic. Cases in this series suggest that such extirpation of the pyogenic focus as can be accomplished clinically does not substantially alter the picture so long as the tuberculous focus remains active. The latter is therefore probably the direct etiologic agent. I have suggested theoretical possibilities relating the pyogenic secondary focus to the production of the cutaneous hypersusceptibility which underlies the pathology of a tuberculid in the hope of stimulating experimental study of a possible association between the two as well as further observation on the clinical existence or non-existence of such an entity. A certain amount of clinical evidence for the ability of a focus of pyogenic infection to produce allergic phenomena in the skin in the form of dermatitides and urticarias is apparently accumulating. The subject of the etiologic relation of focal infection to skin diseases is still so completely in its beginnings, however, that clinical observations can hope as yet to have only suggestive value.

SUMMARY.

1. The material of this study consists of thirty cases of the so-called papulonecrotic tuberculid, of erythema induratum, and of associated conditions constituting, according to the most widely accepted explanation, the allergic response of a hypersensitized skin to emboli of tubercle bacilli from a tuberculous focus elsewhere in the body.

2. Internists and general diagnosticians should find it worth while to familiarize themselves with the essential lesion of these

types of tuberculids, which may prove of great assistance in the recognition of obscure tuberculosis.

3. The tuberculid when not ignored by the general diagnostician is usually confused as shown by this series, with acne and furunculosis, with syphilis, especially if the Wassermann is positive, and on the legs, with acute surgical conditions and ulcus varicosus. Therapeutic tests for syphilis with arsphenamine are misleading in these cases. The diagnostic import of the lesions in obscure lymphadenitis was at times overlooked.

FIG. 19 (197425).—Scar of a healed ulcer, plaque of erythema induratum on the lower portion of the calf.

4. Association with tuberculosis in this series was evidenced by a family history in one-fourth of the cases, incontestible objective signs in more than half (57 per cent.), and presumptive signs of the disease in 70 per cent. One-third of the patients had radiographic signs of pulmonary tuberculosis; an equal number had suggestive or positive physical signs of lung involvement. The importance of lymphatic involvement is illustrated by the fact that two-thirds of them had a tuberculous lymphadenitis.

5. The type and location of the focus of tuberculosis do not seem to influence the tuberculid beyond the marked association with glandular involvement. On the other hand, the influence of vascular

abnormalities and chronic passive congestion in the extremities is very apparent. Ninety-six per cent. of the lesions involved the extremities. Lesions appeared on the ear in 13 per cent.

6. Slight fever at onset, loss of weight in 40 per cent., amenorrhea in 43 per cent. of the women, moderate leukopenia, slight but occasionally severe anemia, and vernal periodicity are the significant signs. An onset and course marked by rheumatic symptoms is very common (46 per cent.) and often misinterpreted. The recognition of the focus of tuberculosis must depend largely upon objec-

FIG. 20 (218126).—Scar of a noduloulcerative syphilid of the pretibial region. Note the arciform, polycyclic configuration.

tive evidence. There is a notable absence of cough, sweats and hemoptysis. Florid, seemingly robust types of patients are not infrequently subjects of tuberculids.

7. Evidence of the importance of a septic focus and collateral types of infections appears from the history of tonsillitis in 39 per cent., "rheumatism" in 46 per cent., pneumonia in 26 per cent., grippe in 54 per cent. and pleurisy in 18 per cent. These conditions seemed frequently to stand in direct predisposing or exciting relation to the tuberculid. A total of 70 per cent. had symptoms and

findings suggesting the presence of a septic focus, and 62 per cent. had had significant respiratory infections excluding pleurisy.

8. While no direct relation of the tuberculid to the clinical condition of the tonsils could be established, 50 per cent. of the patients had markedly septic tonsils, the remainder were passable, and none were normal.

9. Examination of the teeth by *x*-ray in a limited number of the later cases demonstrated the presence of septic foci in 45 per cent. of nine patients. Other foci should be searched for.

10. While the secondary or septic focus was obviously present its influence is obscure. Removal of the tonsils in seven cases failed to prevent the outbreak of a tuberculid or modify its course, and complete extirpation of all recognizable septic foci in two cases, without removing or treating the tuberculous focus, was also unavailing.

11. It is conceivable that the effect of a secondary septic focus, while not direct, is predisposing in that toxins or even bacteria, emanating from it may be in part responsible for the cutaneous allergy which is presupposed in explaining the pathogenesis of the papulonecrotic tuberculid. Evidences of the ability of a septic focus to produce or predispose to dermatitis, urticaria and similar expressions of cutaneous hyperirritability are accumulating. Further indirect evidence of a possible peculiar allergic state of patients with tuberculids is found in reported and personally observed cases of non-specificity in their Wassermann reactions and in their hypersusceptibility to arsphenamin.

REFERENCES.

1. Barthélemy, M.: De l'acnitis ou d'une variété spéciale de folliculites et périfolliculites généralisées et disséminees. Ann. de Dermat. et de Syph., 1891, xxii, 1–38.

2. Boas, H. and Ditlevsen, C.: Untersuchungen über Noguchis Leutinreaktion. Arch. f. Dermat. u. Syph., 1913, cxvi, 852–864.

3. Hempelmann, T. C.: Frequency of tuberculides in infancy and childhood and their relation to prognosis. Arch. Pediat., 1917, xxxiv, 362–365.

4. Jadassohn, J.: Die Tuberkulide. Arch. f. Dermat. u. Syph., 1914, cxix, 10–83.

5. Liebermeister, G.: Zur Frage der öhne Mitwirkung von Tuberkelbazillen erzeugten "tuberkulosen" Veränderungen. München. med. Wchnschr., 1908, lv, 1874–1875.

6. Mayo, W. J.: Secondary tuberculous peritonitis. Its cause and cure. Jour. Am. Med. Assn., 1918, lxxi, 6–8.

7. Meirowsky, E.: Cited by Jadassohn.

8. Nicolas, J., Favre, M., Gautier, Cl. and Charlat, L.: Intredermoréaction avec la syphiline chez les syphilitiques. Lyon méd., 1910, cxiv, 621–630.

9. Petroff, S. A.: Serological studies in tuberculosis. Am. Rev. Tubercl., 1917, i, No. 1.

10. Ravaut, P.: L'action du neosalvarsan et la réaction de Wassermann chez des malades atteints de tuberculides diverses. Ann. de Dermat. et de Syph., 1913, xliv, 470–475.

11. Rist, E., and Rolland, J.: Etudes sur la réinfection tuberculeuse. Troisième mémoire. La réinfection cutanée et le phénomène de Koch. Ann. de méd., 1914, ii, 13–54.

12. Saeves, Inga: Experimentelle Beiträge zur Dermatomykosenlehre. Arch. Dermat. u. Syph., 1915, cxxi, 11-236.
13. Sherrick, J. W.: The effect of potassium iodid on the Luetin reaction; preliminary report. Jour. Am. Med. Assn., 1915, lxv, 404.
14. Snow, C. G. and Cooper, A. T.: The Wassermann reaction in its relation to tuberculosis. Am. Jour. Med. Sc., 1916, cliii, 185–202.
15. Stokes, J. H.: A luetin reaction in syphilis produced by agar, with a brief consideration of its mechanism. Jour. Am. Med. Assn., 1917, lxviii, 1092–1095.
16. Stokes, J. H.: Studies on intradermal sensitization, I. Intradermal reactions to emulsions of normal and pathologic skin. Jour. Inf. Dis., 1916, xviii, 402–414.
17. Stokes, J. H.: Studies on intradermal sensitization, II. An intradermal reaction to agar and an interpretation of intradermal reactions. Jour. Inf. Dis., 1916, xviii, 413–436.
18. Stokes, J. H.: Clinical studies in cutaneous aspects of tuberculosis. I. "Tuberculous" purpura, erythema multiforme and erythema nodosum. Am. Jour. Med. Sc., 1919, clvii.
19. Zieler, K.: Cited by Jadassohn: Hauttuberkulose und Tuberkulide. Prakt. Ergebn. a. d. Geb. d. Haut. u. Geschlectskr., 1914, iii, 17–443.

STUDIES IN A CASE OF ACUTE BICHLORIDE OF MERCURY POISONING TREATED BY THE NEWER METHODS, AND FOLLOWED BY RECOVERY.

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(From the Laboratory of Dr. Jacob Rosenbloom.)

1. Introduction and Review of the Literature. In recent years the treatment of the formerly hopeless cases of bichloride of mercury poisoning has developed along new lines that seem to be of great promise as regards the recovery of these cases.

Lieb and Goodwin[1] emphasized the importance of repeated gastric lavage to remove the mercury excreted into the stomach and Lambert and Patterson[2] have shown the necessity of utilizing every means we have for the purpose of elimination of the mercury from the body. They have shown the necessity of frequent gastric lavage and colon irrigations continued until the washings are free from mercury when tested chemically. Other workers have advised procedures some of which when studied experimentally have failed to protect against mercury poisoning.

Hall[3] recommended the use of a solution of potassium iodide, quinine hydrochloride, hydrochloric acid and water, but Barbour[4] and also Sansum[5] have shown that this antidote is valueless. Fantus[6] has shown that the use of egg albumen is without value unless

[1] Jour. Am. Med. Assn., 1915, lxiv, 2041.
[2] Arch. Int. Med., 1915, xvi, 865.
[3] Jour. Am. Pharm. Assn., 1915, iii, 182.
[4] Jour. Am. Med. Assn., 1915, lxiv, 736.
[5] Ibid., 1918, lxx, 824.
[6] Jour. Lab. and Clin. Med., 1916, i, 879; 1917, ii, 813.

it is given along with or immediately after the poison. He considers lavage with a solution of sodium acetate to be of more value. He also recommends the use of Carter's antidote, a tablet containing 0.36 gram of sodium phosphite and 0.24 gram of sodium acetate. If this is not available he uses a mixture of 5 parts of hydrogen peroxide, 10 parts of water and 1 gram of sodium hypophosphite, using ten times as much hypophosphite as poison and this is followed by copious lavage with the diluted reagent. He also found that sodium bicarbonate had antidotal power, and he uses it in amounts of twenty-five to fifty times the amount of poison taken.

Sabbatani[7] has mentioned the possible value of sulphur, hydrogen sulphide or sodium thiosulphate solutions, as he thinks the use of them as gargles, enemas and hypodermically combat the stomatitis and colitis and impede absorption of the mercury Linhart[8] advises the use of sodium phosphite as an antidote. Wilms[9] considered that the use of calcium sulphide given by mouth and intravenously was of antidotal power in the treatment of these cases. Hayward and Allen[10] also suggested the use of calcium sulphide. Evans[11] a long time ago considered alkalies of use in the treatment of bichloride of mercury poisoning, and recently Hirsch[12] has suggested the use of sodium bicarbonate as an antidote. Burmeister[13] has emphasized the value of repeated venesections and transfusions in the treatment of these cases. Turrettini[14] reports favorably the use of intravenous injections of glucose solution in mercury poisoning. Carter[15] thinks he has successfully treated these cases by giving by mouth a combination of sodium phosphite and sodium acetate to reduce the mercuric salt to mercurous. Sansum[16] has shown experimentally that this method is without value, and Haskell and Courtney[17] have shown experimentally that the intravenous injection of calcium sulphide is too dangerous a procedure to be of value and that its effect is due to the fluid introduced. Schisler[18] has advised the use of magnesium oxide in these cases. Milian and Saint-Avid[19] advised the use of intravenous injections of alkali and

[7] Biochem. Centralbl., 1906, v, 502; Riforma Med., 1907, xxiii, 767; Arch. Int. de Pharmacol., 1907, xvii, 319.

[8] New York Med. Jour., 1913, xcvii, 1236; Jour. Lab. and Clin. Med., 1917, ii, 722.

[9] Jour. Lab. and Clin. Med., 1917, ii, 445; Lancet-Clinic, 1915, cxiv, 555; 1916, cxv, 460; Ther. Digest, 1916, xi, 71.

[10] Jour. Am. Med. Assn., 1913, lx, 1827.

[11] Med. and Phys. Jour., London, 1800, iii, 535.

[12] Chicago Med. Rec., 1914, xxxvi, 444.

[13] Jour. Lab. and Clin. Med., 1917, ii, 500.

[14] Rev. Med. de la Suisse romande, 1915, xxxv, 204.

[15] Chicago Med. Record, 1914, xxxvi, 444; Critic and Guide, 1915, xviii, 266; Am. Jour. Clin. Med., 1914, xxi, 314.

[16] Jour. Am. Med. Assn., 1918, lxx, 824.

[17] Jour. Lab. and Clin. Med., 1917, iii, 110.

[18] Jour. Mississippi Med. Assn., 1917, xiv, 173.

[19] Paris méd., 1917, vii, 213.

glucose. Holm[20] advised the use of calcium sulphide. Macnider,[21] from his studies on the protection that alkalies give to the development of tubular nephritis in uranium poisoning, advises the use of alkalies in acute mercury poisoning. He found that death in acute bichloride of mercury poisoning in dogs was due to shock associated with a mercury enteritis and to delayed kidney damage associated with acidosis. He thought that the delayed kidney injury was not due to the action of mercury as such during its elimination by this organ. Anderson[22] advised water irrigations through a cecostomy wound to hasten the bowel elimination in these cases. Weiss[23] has published a method for treating these cases somewhat similar to that described by Lambert and Patterson, with the exception that the frequent gastric and colonic lavage is omitted. One improvement in his method over that of Lambert and Patterson is that the urine is kept alkaline to a saturated solution of methyl red in alcohol, on the basis that Fischer has shown that if the urine of a nephritic cannot be made alkaline to methyl red this patient continues in a dangerous state.

There is no doubt that the treatment of cases of acute bichloride of mercury poisoning by the newer methods has produced better results than by the former treatment, which was really watching the case until fatal anuria developed. Schisler[24] reports 16 cases with 5 deaths, dose from 3 to 170 grains. Weiss[25] reports 28 cases with 1 death, dose from 3 to 82 grains, the cases being treated by the newer methods.

Brown and Baskett,[26] Lewis and Rivers,[27] and Cohen and Bernhard[28] have reported cases with recovery following the Lambert-Patterson treatment. Nolan[29] has recently presented a very able review of recent work in regard to acute mercuric chloride poisoning. It should be recalled that in the elaboration of any method of treatment of bichloride of mercury poisoning the following conditions are to be met:

The development of anuria, which occurs in from twelve hours up to ten days after taking the poison, due to an acute nephritis and enteritis, and the colitis, due to the inflammation caused by exeretion of the mercury into the intestine. Together with this there exists an acid intoxication, and, as Nolan well says: "The therapeutic problems are (1) to reduce the toxicity of the mercury

[20] Jour. Michigan State Med. Soc., 1917, xvi, 270.
[21] Jour. Med. Research, 1912, xxi, 79; Jour. Exper. Med., 1918, xxvii, 519; 1916, xxiii, 171.
[22] Surg., Gynec. and Obst., 1915, xx, 350; Harrold: Ann. Surg., 1916, lxiii, 127.
[23] Jour. Am. Med. Assn., 1917, lxviii, 1618.
[24] Jour. Mississippi Med. Assn., 1917, xiv, 173.
[25] Ohio State Med. Jour., 1917, xiii, 595; Jour. Am. Med. Assn., 1917, lxviii, 1618.
[26] Jour. Am. Med. Assn., 1917, lxviii, 1622.
[27] Johns Hopkins Hosp. Bull., 1916, xxvii, 193.
[28] Jour. Am. Med. Assn., 1916, lxvii, 1019.
[29] Interstate Med. Jour., 1917, xxiv, 997.

in the system; (2) if possible to hasten its elimination; (3) to combat the acid intoxication and its attendant evils.

That some method to facilitate the elimination of the mercury present in the body is needed is shown by the following data. In a case of bichloride of mercury poisoning in which death followed ten days after taking the drug I[30] was able to find the following amounts of mercury still present in the body:

Organ.	Mercury present in milligrams.
Kidney	5.8
Spleen	1.7
Liver	39.82
Brain	1.68
Stomach	1.50
Small intestines	4.80
Large intestines	7.28
Heart	5.81
Lungs	trace
Blood	52.2
Muscle	25.8
Bile	trace
Stomach contents	12.2
Intestinal contents	8.6
Rectal contents	8.4

Some recent experimental work of Sansum[31] seems to show that when an amount of mercuric chloride in excess of 4 mg. has entered the tissues at large, death regularly occurs, and that we have no adequate grounds for believing that death is preventable by any known form of treatment. He thinks that therapeutic efforts should be directed toward the mechanical removal of the poison from the lumen of the alimentary tract and antidoting the poison before it leaves the portal circuit—that is, particularly before absorption. However, Sansum does not take into consideration the treatment of the acidosis present in these cases.

2. Case History. A man, aged thirty-five years, physically well but mentally sick, chewed up three 7½-grain tablets of bichloride of mercury at twelve o'clock noon. He vomited at two o'clock, and the vomitus contained streaks of blood. He was given, at three o'clock, the whites of three eggs and a quart of milk, and this was vomited in ten minutes. The treatment outlined in this paper was started at seven o'clock—that is, seven hours after the poison was taken. During the first two days the bowels moved every two or three hours and the movements contained shreds of mucus and blood. The stomach washings also showed clumps of clotted blood during this time; a severe stomatitis developed on the third day. Excruciating lumbar pain came on during the second day and lasted for three days. At the end of the first week I felt confident that the patient would recover. He was carefully watched for one month

[30] Rosenbloom: Jour. Biol. Chem., 1915, xx, 123.
[31] Jour. Am. Med. Assn., 1918, lxx, 824.

and was discharged as completely recovered. He is at present (twelve months after his illness) well in all respects and no trace of damage to his kidneys can be found by examining his urine or by testing the kidneys by the functional methods.

The following tables contain the data obtained in the study of this case of acute bichloride of mercury poisoning:

TABLE I.—ANALYSES OF BLOOD.

Day.	Total non-protein nitrogen. Mgm. per 100 c.c. blood.	Urea nitrogen. Mgm. per 100 c.c. blood.
1	42	20
2	48	25
3	84	66
5	140	94
8	172	140
10	176	138
12	141	100
14	92	70
17	60	40
20	48	25
22	40	20
24	36	18
25	32	12
28	28	11
30	23	10

3. LABORATORY STUDIES. Foster,[32] Phillip,[33] Myers and Lough,[34] Squier and Myers,[35] Campbell and Hunter,[36] Woods,[37] and Lewis and Rivers[38] have published chemical studies of the blood in bichloride of mercury cases. When my results are compared with those obtained by these observers it may be noted that at no time did the blood non-protein nitrogen or urea-nitrogen reach the high values found by some of these workers. I consider that the lower values obtained in this case were due to the better excretion by the kidney, owing to the treatment used. However, there is a marked increase in the non-protein nitrogen and the urea-nitrogen of the blood in acute bichloride of mercury poisoning.

DISCUSSION OF TABLE II. The presence of large amounts of acetone and diacetic acid in the urine with the high ammonia nitrogen points to the existence of a definite acidosis. That an acidosis exists in uremia was shown long ago by von Jaksch.[39] Straub and Schlayer,[40] Sellards,[41] Palmer and Henderson,[42] How-

[32] Arch. Int. Med., 1915, xv, 755.
[33] Med. Klinik, 1913, ix, 912.
[34] Arch. Int. Med., 1915, xvi, 536.
[35] Jour. Urol., 1918, ii, 1.
[36] Jour. Biol. Chem., 1917, xxxii, 195; 1918, xxxiii, 169; Arch. Int. Med., 1917, xx, 919.
[37] Arch. Int. Med., 1915, xvi, 577.
[38] Johns Hopkins Hosp. Bull., 1916, xxvii, 193.
[39] Ztschr. f. klin. Med., 1889, xiii, 350.
[40] München. med. Wchnschr., 1912, lix, 569.
[41] Johns Hopkins Hosp. Bull., 1914, xxv, 141.
[42] Arch. Int. Med., 1915, xvi, 109.

land and Marriott[43] and Peabody[44] have also found an acidosis present in uremia. However, this case shows that there was an overproduction of acid bodies and that the acidosis was not entirely due to an imperfect excretion of the acid radicals, as is claimed by Palmer and Henderson. The existence of this acidosis shows the necessity of treating cases of bichloride of mercury poisoning with this factor in mind. It shows the necessity of using the low protein, low fat and high carbohydrate diet and the use of alkalies to keep the urine persistently alkaline to methyl red. It may be noted that on the twenty-fourth day of the illness all damage to the kidney had been repaired, as evidenced by changes in the urine. From this day on the urine was normal in all respects. The acidosis was kept under control by the use of alkalies, glucose and high carbohydrate, low protein and low fat diet. I think that the control of the acidosis was an important feature in the successful outcome of this case.

TABLE II.—ANALYSES OF THE URINE.

Day	Volume, c.c.	Sp. gr.	Reaction.	Protein gm. per liter.	Nitrogen gm.	Ammonia nitrogen.		Acetone.	Diacetic acid.	Microscopic.				
						Gm.	Per cent. of total Nitrogen.			Hyaline casts.	Granular casts.	Red blood cells	White blood cells	Epithelial cells.
1	300	1010	Acid	3.5	3.8	0.22	6.0	xxxx	xxxx	xx	xx	xx	xx	xxx
2	420	1008	Acid	4.0	3.9	0.23	5.8	xxxx	xxxx	xx	xx	xx	xx	xx
3	880	1009	Acid	4.0	5.2	0.53	10.2	xxxx	xxxx	xx	xx	xx	x	xx
4	1600	1010	Acid	1.0	6.2	0.90	14.5	xxxx	xxxx	xx	xx	xx	x	xx
5	3000	1012	Acid	1.0	7.1	0.89	12.6	xxxx	xxxx	xx	xx	xx	x	xx
6	4200	1010	Alkaline	0.5	8.1	0.73	8.9	xxxx	xxxx	xx	xx	xx	x	xx
7	4800	1010	"	0.5	7.2	0.91	12.7	xxx	xxx	xx	xx	xx	x	xx
8	6000	1010	"	0.5	10.4	1.00	9.6	xxx	xxx	x	x	xx	x	xx
9	6400	1012	"	Trace	11.6	1.03	8.9	xx	xx	x	x	xx	x	x
10	5200	1010	"	"	10.8	0.93	8.6	xx	xx	x	x	xx	0	x
11	5000	1009	"	"	9.7	0.78	8.1	xx	xx	x	x	x	0	x
12	4840	1010	"	0.5	10.2	0.82	8.0	xx	xx	x	x	x	0	x
13	3200	1012	"	0.5	10.3	0.77	7.5	x	xx	x	x	x	0	x
14	3000	1014	"	Trace	9.8	0.72	7.4	x	x	x	x	x	0	x
15	1500	1015	"	"	9.4	0.61	6.5	x	x	x	x	x	0	x
16	1420	1018	"	"	8.6	0.53	6.2	x	x	x	x	x	0	x
17	1400	1016	"	"	7.2	0.44	6.1	0	0	x	x	x	0	0
18	1200	1015	"	"	6.8	0.35	5.1	0	0	x	x	x	0	0
19	1100	1010	"	"	7.4	0.39	5.3	0	0	x	x	x	0	0
20	1000	1018	"	"	7.2	0.36	5.0	0	0	x	x	x	0	0
21	1860	1012	"	"	7.0	0.41	5.8	0	0	x	x	x	0	0
22	1500	1012	"	0	6.8	0.32	4.7	0	0	x	x	x	0	0
23	1450	1014	"	0	5.6	0.25	4.5	0	0	x	x	x	0	0
24	1860	1010	"	0	5.8	0.29	5.0	0	0	0	0	0	0	0
25	1010	1016	"	0	7.2	0.37	5.1	0	0	0	0	0	0	0
26	1200	1015	Acid	0	7.1	0.37	5.2	0	0	0	0	0	0	0
27	1280	1018	"	0	8.6	0.55	4.6	0	0	0	0	0	0	0
28	1400	1017	"	0	8.4	0.40	4.8	0	0	0	0	0	0	0
29	1030	1014	"	0	7.6	0.34	4.5	0	0	0	0	0	0	0
30	1200	1018	"	0	7.2	0.32	4.4	0	0	0	0	0	0	0

[43] Johns Hopkins Hosp. Bull., 1916, xxvii, 63.
[44] Arch. Int. Med., 1914, xiv, 236; 1915, xvi, 955.

TABLE III.—PHENOLSULPHONEPHTHALEIN TEST.

Day.	Per cent. of dye excreted in the First hour.	Second hour.	Total.
1	trace	trace	
2	trace	trace	
3	5	5	10
5	10	5	15
8	15	10	25
10	18	12	30
12	20	15	35
14	18	18	36
17	20	18	38
20	25	20	45
22	30	20	50
24	35	20	55
25	35	15	50
28	40	20	60
30	40	20	60

Discussion of Table III. This table shows very nicely the damage done to the kidneys by the bichloride of mercury and the gradual resumption of the kidney function in the later days of the illness. From the merest trace of the dye being excreted on the first and second days following the ingestion of the mercury, the amount gradually increased until on the twenty-second day it could almost be considered normal and on the twenty-eighth day the excretion of the dye was normal.

TABLE IV.—STUDIES OF THE MERCURY EXCRETED.

Day.	Mercury present in: Urine.	Colon washings.	Gastric washings.
1	xxxx	xxxx	xxxx
2	xxx	xxx	xxx
3	xxx	xxx	xxx
5	xxx	xxx	xxx
8	xxx	xxx	xxx
10	xxx	xx	xx
12	xx	x	x
14	x	x	x
17	x	x	x
20	x	x	x
22	Trace	Faint trace	Faint trace
24	Faint	" "	" "
25	"	Very faint	Absent
28	Absent	Absent	"
30	"	"	"

Discussion of Table IV. The necessity of continuing the treatment of these cases for a long period of time is clearly shown by a study of this table. Fairly distinct amounts of mercury were still present in the urine, colon washings and gastric washings for a period of twenty days following the ingestion of the mercury. Faint traces were still present up until the twenty-eighth day. There is no doubt that the best method is to continue the treatment used in these cases until the urine, the colon washings and the gastric washings are free from mercury.

The method of treatment that was used in this case was a combination of various procedures that have been advised for the treatment of mercury poisoning. It may be tabulated as follows: In this case the sodium phosphite and sodium acetate were not used, instead the hypophosphite-peroxide mixture was used.

Method of Treatment to Be Used in Cases of Bichloride of Mercury Poisoning.

1. Administer the whites of three eggs beaten up in a quart of milk and then empty the stomach by siphonage.

2. Give 300 c.c. of fresh calcium sulphide solution, containing 1 grain to 1 ounce of water by mouth.

3. Wash out the stomach with fresh calcium sulphide solution, 1 grain to 1 ounce of water.

4. Administer in powder or tablet 0.36 gram of sodium phosphite and 0.24 gram of sodium acetate. If this is not available give the following:

Sodium hypophosphite	1 gram
Water	10 mils.
Hydrogen peroxide	5 mils.

Use ten times as much of the hypophosphite as poison taken. Give a copious lavage of stomach with the above antidote diluted twenty times. Give the above undiluted antidote every eight hours for two days.

5. Pour through the stomach tube after the above lavage a solution of 3 ounces of sodium sulphate and 6 ounces of water containing 5 grains of calcium sulphide. Let these solutions remain in the stomach.

6. Give intravenously after withdrawing 600 c.c. of blood, 800 c.c. of Fischer's solution or of bicarbonate-glucose solution.

7. Wash out the stomach morning and night, giving by the mouth after each washing, 5 grains of calcium sulphide dissolved in 3 ounces of water. Continue this lavage until the stomach washings are free from mercury when tested by Elliott's[45] method and until the urine is free from mercury.

8. Give high colon irrigations of warm water morning and night, using 8 gallons of the water for each treatment.

9. Give a hot pack twice daily.

10. Give 8 ounces of milk every second hour.

11. Give every second hour 8 ounces of the following solution, by mouth, alternating with the milk:

Potassium bitartrate	dr. j
Sodium citrate	dr. j
Sucrose	dr. j
Lactose	dr. iv
Lemon juice	oz. j
Boiled water	oz. xvj

[45] Jour. Am. Med. Assn., 1917, lxviii, 1693.

12. Force the patient to drink large quantities of the alkaline waters, such as Celestin's Vichy or Kalak water.

13. Give a low fat and low protein and high carbohydrate diet for four weeks. Avoid salt in food, as it increases the absorption of the mercury.

14. Give by continuous proctoclysis a solution containing 1 dram potassium acetate, 4 drams glucose and 3 drams sodium bicarbonate to the pint.

15. Keep the urine alkaline to methyl red.

16. Continue rest of treatment until recovery, usually a period of three weeks.

7

A CASE OF BULIMIA, WITH REMARKS ON THE CAUSAL TREATMENT OF SOME FUNCTIONAL DISEASES.[1]

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Though bulimia is always mentioned in the proper connection, it rarely gets into indexes, and does not seem to be very frequent in practice. The descriptions in text-books are as a rule very good, but the tendency to place bulimia with polyphagia in diabetes or exophthalmic goitre must raise doubt in the mind of anyone who sees a case like the one I report, or even one who reads a current definition, as to its place in pathology. Recent studies of hunger, especially those of Cannon and Carlson and their collaborators, give an added interest to all anomalies of hunger. For these reasons and on account of the outcome of the case, I report the history of a patient sent me recently for investigation.

G. S., aged thirty-six years, architect.

Diagnosis. Bulimia, pansinusitis, acute rhinitis, pharyngitis and laryngotracheitis, caries of teeth, alveolar abscess.

Complaint. The patient has to eat more frequently and in larger quantities than normal. Hunger attacks begin with general feeling of uneasiness, followed, if food is not taken, by an intense headache, generally in the eyes or frontal region. Sometimes headache comes quickly if food is not taken, sometimes it is delayed. The patient eats from five to fifteen times in twenty-four hours. More accurately, he has no regular meal time and does not always eat with the family, but eats at any time he feels a craving. At family meals he may take a bowl of soup, crackers, rice or bread. He has acquired the habit of eating toasted bread cubes, which he always has with him in large tin cans. He will eat a bowlful of these, or five to eight shredded wheat biscuits each time he gets hungry.

[1] Read before the Association of American Physicians, Atlantic City, May 7, 1918.

Family History. Mother and two sisters died of cancer of stomach. Father and one sister living and well. No history of tuberculosis, arthritis, constitutional or nervous disease.

Previous History. As an infant, patient had digestive disorders, according to a statement from his mother, and up to seven years had an idiosyncrasy to bananas. From seven to twenty-one he was always well. About twenty-one, while at college, he overworked, and at one time was ill two weeks with "gastritis and pleurisy." He lost weight from 175 to 135 pounds. There were then recurring attacks, following fatigue or overwork, but gradually becoming less frequent. These attacks began with a chill, followed by abdominal distention, pain through the chest, radiating to the back, causing the patient to double up. There were eructations, which seem to have suggested the name "gastritis" for the attacks. After the last attack, five years ago, the patient followed a diet composed of easily digested food. At the age of twenty-two the right arm became paralyzed and remained so for two years, but gradually recovered. The cause was not clearly made out, though the patient was examined by several distinguished neurologists. The final opinion expressed was that the paralysis was due to sleeping on the arm.

In February, 1918, he had an infection in the head, spoken of as "grip," since which time the nose has been obstructed. The patient seemed to have been almost wholly free from subjective symptoms, and had no severe sinusitis symptoms. Later, he gave a history of "catarrh," for which the nose was treated when he was sixteen. Since then he has kept the nose clear by snuffing up salt solution. He had no idea the condition was severe and was not aware of his nasal voice. He had always led an active life, riding and walking much, playing tennis, association football and hockey. No abuse of alcohol. No history of venereal disease.

The present trouble (voracious appetite) dates from January, 1915. At first he felt hungry about 9 P.M., and would eat a bowl of rice or something similar. The condition gradually grew more severe.

Three years ago he weighed 145 pounds. He now weighs 215 pounds. In the last six weeks he has grown short of breath. When the amount of food is large the bowels are loose.

The hands have not become larger. Does not think there is any change in shape or size of head.

The present diet has been described. The amount of water consumed varies with the food, but is always more than normal. The amount of urine seems increased, but has not been measured.

The patient has been under the care of various physicians. Recently, under the view of a ductless gland disease, he was treated in turn with dried thyroid, adrenalin and pituitary preparations. The first had no effect, but the others seemed to give relief and reduced the appetite. Had also taken tincture of belladonna up to

20-drop doses. The throat got very dry and the symptoms were checked for about a day, but returned. Patient has washed out his stomach with a tube, daily for a week, with benefit. He found that bulky vegetables relieved hunger longer than meat. He can eat all kinds of food. Sometimes a small amount of food satisfies; at times he cannot eat enough.

Physical Examination (February 9, 1918). Man of large, heavy frame, well formed. Panniculus moderately thick; no abnormal fat distribution.

The skin is warm, pink or mottled when stripped in a rather cool room. Patient does not object to the cold. The lips and finger tips are slightly cyanotic. The abdomen shows white lines from the pressure of the bedclothes. Nail scratch brings out white lines, remaining several minutes. Gentle stroke with finger brings out broad white line, also lasting several minutes. The scalp hair is thin in front. Eyebrows and beard (shaved) heavy. Body hair scanty; semifeminine escutcheon.

The supra-orbital prominence, malars, nose and chin of good size, but not pathological. The voice is nasal obstructive; the nose is obstructed and shows pus in the anterior nares. The teeth are well shaped, unusually regular and not spaced. Five molar teeth are decayed to the roots. The other molars and the bicuspids are extensively repaired, but show several cavities. The gums are swollen and reveal exudate in several places. The patient explained the bad condition of his mouth by saying he could not abstain from eating long enough to let a dentist work on him.

The tongue is not large. The posterior wall of the pharynx is covered with tenacious yellow mucopus.

The thyroid is not palpable.

Thorax broad, deep and symmetrical. Expansion good. Auscultation and percussion of lungs negative.

The heart impulse is not visible or palpable. Dulness extends 11 cm. to the left in the fifth interspace, $2\frac{1}{2}$ cm. to the right in the third, 2 cm. in the fourth. The first sound at the apex is impure. There is a soft blowing systolic murmur in the aortic area. Aortic second sound accentuated. The radial pulse is of good volume. Blood-pressure, 188 to 92.

The abdomen is above the level of the ribs, the wall thick and firm. Liver and spleen not palpable.

The right arm is smaller than the left, 30.5 cm. as compared with 31.5 cm. at the insertion of the deltoid. Both forearms equal; right grip weak, the thumb and index only being affected by the weakness, but with little atrophy. The right hand is paler than the left.

The reflexes are normal.

Some small hemorrhoids, otherwise rectal examination negative.

Blood: Hemoglobin, 90; red blood corpuscles, 6,600,000; leukocytes, 5600.

Wassermann tests, blood and spinal fluid negative. Five cells per cubic millimeter in the spinal fluid. Ross Jones negative.

Urine: Admission specimen, clear, light yellow. Specific gravity, 1010; acid; no sugar; no albumin. Phenolsulphonephthalein test, 10 min. trace; 1 h. 10 min., 25; 2 h. 10 min., 22; total, 47 per cent.

Blood chemistry, February 9: Non-protein nitrogen, 30.1 mg. per 100 c.c. Urea, 13.2 mg. Sugar, 0.0495 gm. per 100 c.c.

Examination of stomach contents: Vomitus on passing tube; about 200 c.c.; semisolid; no mucus; no blood; HCl, 24; total acidity, 46. No lactic acid. No bacilli, yeasts or sarcines. Fat and starch present.

Test-meal, shredded wheat biscuit: Free HCl, ½ h., 35; 1 h., 20; 1½ h., 20; 2 h., 35; 2½ h., 30; 3 h., 25. Total acidity, ½ h., 55; 1 h., 60; 1½ h., 45; 2 h., 55; 2½ h., 40; 3 h., 40.

Stool: (February 9), 410 grams, formed, dry. Large amount of shredded wheat biscuit like coarse bran; no mucus, blood or pus.

The first night the patient was in the hospital orders were left to give him anything he asked for. Between 8 P.M. and 6 A.M. he took 800 c.c. of milk; 5000 c.c. of water and 16 shredded wheat biscuits, besides some bread cubes; calories, 1684. The next twenty-four hours he took total calories, 7038.4.

These quantities of food were not considered excessive by the patient. They were lessened by the further examinations, so that we had no opportunity for seeing the possibilites in that way.

February 10. The blood examination gave non-protein nitrogen, 25 mg. per 100 c.c.; urea, 16 mg. per 100 c.c. Blood-pressure, 160 to 90. White line as before.

Sugar tolerance in blood tests: before test, 0.087; ½ h. after, 200 grams glucose, 0.170; 1 h., 0.115; 1½ h., 0.105; 2 h., 97; 2½ h., 95. No sugar in urine at any time.

URINARY CONDITIONS DURING OBSERVATIONS.

February	9	Amount	3800	N	9.98	NH_3N 0.863
"	10	"	4645	N	16.29	NH_3N 1.98
"	11	"	2900	N	16.40	NH_3N 2.01
"	12	"	2400	N	14.61	NH_3N 1.90
"	13	"	1800	N	14.37	NH_3N 1.78

Skiagram of head, stereoscopic, shows large frontal sinuses; posterior half of skull very thick, especially inner plate. Sella small, shallow. Appearance as of bridge of bone across top.

Films of teeth show periapical infection of two teeth and suspicious areas around several others. Referred to dentist.

Examination of nose and throat by Dr. C. A. Gundelach, February 11: Left nasal chamber entirely occluded by several polyps. Right chamber filled with pus. Evident middle and superior meatus suppuration. Nasopharynx greatly infected; pharynx also. Tonsils

small; submerged; chronic tonsillitis. Lingual tonsil considerably hypertrophied. Larynx and trachea show acute inflammation.

February 11. Roentgen-ray examination, gastro-intestinal, by Dr. R. W. Mills (abstract): Stomach rather atonic; is large in all dimensions; gastric tonus fairly good only; pyloric tonus fairly good. Gastric motility no more rapid or slower than normal. No initial clearance. Cap perfect; ring perfect. At four and three-quarter hours stomach empty. Barium in terminal ileum and ascending colon. Barium enema shows cecum and entire colon of rather large dimensions; takes one-third more enema than usual. No definite evidence of colonic hypermotility. No abnormalities in or about appendix.

The patient became restless while the various tests that prohibited eating were carried on. It soon became clear that diabetes and organic stomach disease, intestinal disease and intestinal parasites and pancreatic disease could be ruled out. Pituitary disease and disease of the central nervous system seemed possible to exclude, also neurasthenia and hysteria.

The condition of the teeth and the nose and accessory cavities indicated something more than symptomatic treatment. The character of the food eaten between meals made one think of relief to reflex irritation, and the mouth and nose seemed possible sites of such irritation. I therefore advised the patient to have the local diseases treated at once, stating that this might stop the chief symptoms; if not, further investigations into metabolism were agreed to by the patient.

Work on the mouth was begun by Dr. Wm. B. Spotts, dentist in the medical service, and on the nose by Dr. Gundelach. The hopelessly defective teeth were extracted and the infections treated. The nasal polyps were removed, the largest three-quarter inch in diameter. Both antra were opened nasally and all the sphenoidal and ethmoidal sinuses and large quantities of foul pus washed out.

By March 5 the patient reported himself very much improved. "He eats three times a day, and though sometimes hungry is much less so than before. He looks well, but his voice is still somewhat nasal."

April 4. Nose almost well. No voracious appetite for a month, except once, and then not bad. No hunger at night. Feels much better in every way. Weight, 190 pounds. No white line, only a red line fading rather rapidly.

May 1. Feels well. Weight, 185 pounds. Large appetite only once since last visit; none at night.

There was no opportunity to make observations such as Carlson made with such advantage with intragastric balloons, so that we cannot tell the details of the hunger contractions. But it seems certain from the roentgen rays as well as the clinical observations that rapid emptying of the stomach had nothing to do with the

hunger pain. Attractive as this theory of bulimia is, it seems that it must be an infrequent explanation, from negative evidence. In patients with cancer of the cardiac end of the stomach, with rapid, sometimes instantaneous emptying, hunger has not been present. My roentgenologic colleague, Dr. R. W. Mills, tells me he has not seen it in any of some 25 cases of rapid emptying after gastro-enterostomy.

It is perhaps going too far to assert that the treatment was the cause of the improvement. Many will think the condition was a neurosis and the improvement a coincidence, perhaps only temporary. However that may be, I think the case has a lesson in showing the advantage of treating local diseases that may cause functional disorders rather than resorting to the narcotics, depressants or other symptomatic remedies still recommended and used in such cases.

The case illustrates another feature of therapeutics. For years medical teachers have emphasized the importance of "treating the patient and not the disease," of ascertaining the complete anatomical and functional condition of the patient and correcting all anomalies. This would seem to mean that all morbid processes should be treated, instead of treating abstract conceptions.

Focal infections, sometimes causing local symptoms, always capable of setting up other and dangerous processes, would seem to indicate careful and exhaustive treatment. And yet we see all kinds of neuroses in patients with infections of the teeth, tonsils, prostates, or appendices, but little or nothing done with the demonstrated foci unless a haphazard effort with vaccines.

A STUDY OF MIGRAINE.

By Mary P. S. Rupert, M.D.,

and

Elizabeth E. Wilson,

Philadelphia.

An eminent English neurologist has said: "There is no problem that requires more thorough and searching investigation than the origin of headaches, and there is no condition so unimportant that it can be overlooked in any case of headache."

With the above axiom in mind, the work on the study of migraine was undertaken—to find the origin of the disturbance, and if possible to correct it. In a condition so varied, the lines presenting for investigation are indeed numerous, and, we believe, none are too trifling to be passed by.

Migraine is the commonest of all forms of headache. This is hardly disputable by anyone who takes the trouble carefully to investigate the history. On the whole, more women than men are attacked—the proportion about 6 to 4—and social status seems to exert very little influence, as one finds the condition as frequently in the poor as in the idle rich. On the other hand, it is probable that brain workers in consequence of their mode of life are more frequently and severely visited than those whose business is in the open air.

The symptoms begin usually in childhood. In individual cases, however, the condition makes its appearance only in the third or fourth decade. If the onset is given with certainty as late as this, the diagnosis should be made with caution.

There are few ills which depend to the same degree as migraine upon direct homogeneous heredity. Moebius, indeed, found that 90 per cent. of his cases showed direct heredity. This point is of great theoretical and practical interest.

The predisposition to hemicrania must be distinguished from the exciting causes of the outbreaks, and frequently the first attack follows one of the infectious diseases, typhoid, scarlet fever, influenza and the like. Among the actual exciting causes of individual attacks are: emotional disturbances, anger, any mental overexertion and alcohol. Constipation and menstruation play a very important role. It is a fact that disease of the mucous membrane of the nose and accessory cavities and of the ears, as well as irregularities of the eyes, will precipitate attacks. Migraine not uncommonly accompanies a patient throughout life, although with considerable intermissions.

This condition so prevalent among us has been known since the time of Hippocrates, and derives its name from the Greek word, which means hemicrania. It was so named by Galen.

In contradistinction to the word *hemicrania*, the pain is not necessarily so limited, and, indeed, in certain cases of migraine there is no headache at all.

Migraine is not a disease entity, but rather a symptom-complex occurring in various forms and intensity in different people.

In order to provide a background, we shall use a modification of the classification as given by Flateau.

1. Migrainus Vulgaris. This is a frequent form, accompanied by pressure in the head, lassitude, anorexia and nausea. The eye symptoms and actual pain may or may not be present. This type rarely has an aura.

2. Ophthalmic Type. The symptoms are legion, but the striking and ever-present few which may make the diagnosis for the doctor when seeing the patient are: sensitiveness to light and noises, with scotoma scintillans; exquisite pain in the head, not necessarily limited to a hemicrania, but felt over the entire head,

with aching in the jaws, the nose and the occiput region. This type is accompanied by nausea and vomiting and great prostration during the attack. Paralysis of individual ocular muscles sometimes occurs during the attack, with some resulting ptosis.

3. VASOMOTOR TYPE. This has, if possible, more symptoms to its credit than the ophthalmic variety, and among them may be included: hemicrania, or diffuse pain; angioneurotic edema; abdominal pain; disturbances of peristalsis; cardiac depression; breathlessness; yawning or sneezing, with marked dizziness.

4. PSYCHICAL MIGRAINE. Psychical migraine differs from the vulgaris type in that it has marked psychical disturbances within physiological limits, such as temporary loss of memory, temporary aphasis, hysterical spasm, garrulousness and melancholia.

Pathology has shown no demonstrable lesion; therefore, the cause has been the subject of innumerable speculations. It may be readily understood how such varied symptoms in so many parts of the body lead to varied hypotheses. It would seem to us the theories most worthy of mention are:

The Reflex Theory. This is based upon the idea that the condition is produced by a reflex stimulation of some important organ, such as the uterus, eye, nose, stomach and the like.

The Vasomotor Theory. The vasomotor theory depends upon the vasomotor processes and upon arterial hyperemia. In this theory certain groups of symptoms are explained also by venous or passive congestion, while still others are to be accounted for by weakened functional control. These changes may cause marked vascular contractions or the so-called angiospastic form.

The Central Theory. The central theory would prove the process as primarily in the brain substance, the principal factors being hyperemia or congestion of the brain cortex and meninges. Spritzer suggests that an excessive secretion of the choroid plexus is associated with either a functional or anatomical stenosis (partial or complete) of the foramen of Monro and a subsequent congestion of the brain. Deyl believes a swelling of the hypophysis to be the underlying factor. Quincke holds that an angioneurosis causes increased brain-pressure and Schulke introduces the colloid theory in attempting to account for too much brain substance for the skull capacity. However interesting these points may be they are entirely hypothetical, and careful histological-anatomical examinations have not confirmed them.

The Toxic Theory. The toxic theory presupposes some disturbance of metabolism, and most frequently mentioned is gout in its so-called neuroarthritic form, or a disturbance of the endocrine system, or a combination of both.

ANALYSIS. Consideration of all these views leads to the conclusion that the symptoms of migraine arise from stimulation of certain areas in the central nervous system and that this stimu-

lation may be provoked in many ways: by pressure, by reflex stimulation or by circulation in the blood of certain toxic materials, the nature of which has not been satisfactorily determined.

It is with the last named that our studies have been chiefly concerned. With this factor in view we have tried to find a possible source of poison.

Case No.	Age.	Heredity.	Age at onset.	Frequency of attacks.	Possible contributory factors.
1	38 years	Migraine; carcinoma	20 years	Every three or four weeks	Chronic tonsillitis.
2	24 years	Negative	22 years	Two or three times a week	Astigmatism.
3	56 years	Negative	18 years	Every two or four weeks	Pyorrhea and dental caries; cholelithiasis (operation three years ago); eye trouble.
4	32 years	Syphilis; tuberculosis	18 years	Every two weeks	Artificial menopause.
5	45 years	Negative	20 years	Every ten days	Pyorrhea.
6	48 years	Tuberculosis	25 years	Once a week	Pyorrhea.
7	36 years	Negative	14 years	Once in two weeks	Cervical lymphangitis. pyorrhea.
8	40 years	Carcinoma	33 years	Once a week	Goitre; cholelithiasis (operation one year ago); pyorrhea.
9	33 years	Rheumatism; chorea	26 years	Once or twice a week	Spur in nose.
10	22 years	Tuberculosis	Childhood	Irregular, associated with unusual mental strain	Astigmatism and strabismus.

Case No.	Wassermann.	Blood count.	Routine urinalysis.				Blood-pressure.	
			Sp. gr.	Albumin	Casts.	Indican.	Systolic.	Diastolic
1	Negative	Normal	1021	−	+	+	100	74
2	Negative	Normal	1030	−	−	−	92	62
3	Negative	Normal	1027	−	+	+	176	93
4	Negative	Normal	1011	−	−	−	101	65
5	Negative	Normal	1032	+	−	+	116	72
6	Negative	Normal	1021	+	−	+	120	75
7	Negative	Normal	1012	−	−	−	100	70
8	Negative	Normal	1015	−	−	−	113	69
9	Negative	Normal	1015	+	+	−	113	68
10	Negative	Normal	1013	+	−	−	118	72

In each case a careful study has been made of the gastric contents and the feces. The problem of nitrogen retention was studied by the quantitative estimation of urea in the blood, and the kidney function was investigated by the tests which have been accepted as most dependable, *i. e.*, the phthalein and the Mosenthal test diet.

To eliminate other possible factors and to round out a complete study of the case we have included the Wassermann test, the blood count and routine urinalysis. A careful history has been taken of each patient and a thorough physical examination made in a search for predisposition and for an exciting cause.

In the course of the physical examination we have noted that many cases of migraine run an abnormally high blood-pressure

during the attack; therefore, we have made a careful study of this particular phase of the subject, estimating the blood-pressure both during and between the attacks.

It has been interesting as well as significant to find that each case having frequent and severe attacks of migraine shows, then, *some abnormality of the stool, usually putrefaction, with an alternation of blood-pressure, and these are usually accompanied by delay of kidney function with some disturbance of nitrogen output.*

Case No.	Specific gravity, range.	Examination of												Result.	Blood urea.
		Fluids.				Chlorides.				Nitrogen.				Kidney function.	Milligrams per liter.
						Day.		Night.		Day.		Night.			
		Day.	Night.	Total.	Result.	Grams.	Per cent.	Grams.	Per cent.	Grams.	Per cent.	Grams.	Per cent.		
1	23	864	170	1034	Normal	9.67	1.16	1.68	0.90	4.95	0.55	2.38	1.40	Normal	85
2	8	1448	620	2068	Poor	7.30	0.50	1.90	0.30	11.60	0.80	8.00	1.30	Poor	890
3	8	1074	670	1744	Fair	5.47	0.50	3.90	0.58	12.00	1.10	0.13	0.20	Poor	240
4	14	1140	640	1780	Fair	3.30	0.29	2.04	0.32	5.01	0.44	4.16	0.65	Poor	160
5	23	804	620	1424	Poor	5.50	0.69	1.98	0.32	5.64	0.70	6.01	0.97	Fair	120
6	17	1178	580	1758	Normal	5.30	0.44	2.61	0.45	6.60	1.70	6.50	0.90	Normal	119
7	6	902	603	1532	Poor	9.49	0.78	1.60	0.39	5.23	0.80	3.21	0.51	Fair	300
8	6	1378	550	1928	Poor	6.33	0.46	1.18	4.96	4.96	0.36	1.76	0.32	Poor	280
9	18	1086	722	1808	Normal	4.67	0.40	3.82	0.40	3.69	0.34	2.02	0.28	Normal	310
10	13	680	692	1372	Poor	4.48	0.65	3.80	0.54	3.73	0.54	4.13	0.59	Poor	230

Case No.	Renal function. Phenolsulphonephthalein test.			Gastric contents.	Feces.	Results.
	1st hour.	2d hour.	Total.			
1	18.0	8.5	26.5	Hyperacidity (mild)	Putrefaction	Improved.
2	14.0	15.5	29.5	Normal	Putrefaction	Improved.
3	21.0	16.5	37.5	Normal	Putrefaction	Improved.
4	14.0	8.0	22.0	Normal	Putrefaction	Improved.
5	22.0	17.5	39.5	Normal	Putrefaction	Improved.
6	27.5	13.5	41.0	Normal	Acid fermentation	Improved.
7	28.0	15.5	43.5	Hypersecretion	Putrefaction	Improved.
8	11.0	10.5	21.5	Normal	Putrefaction	Not improved.
9	41.0	15.5	56.5	Normal	Putrefaction	Improved.
10	14.5	12.5	27.0	Normal	Acid fermentation	Not treated.

Our own clinical observations confirm those of other investigators who find unusually high blood-pressure readings during the attack and varying blood-pressure readings in the intervals of the attack, either high or low.

We have further found that this variation of blood-pressure between attacks corresponds with the findings in the stool. For instance, a persistently low blood-pressure reading is apt to be associated with an excessively putrefactive movement, and as the stool condition is corrected, the attacks are less in frequency and

severity, and some cases show improvement in pressure between attacks.

What, then, is the source of the irritation? Our next work on this will be an attempt to find the possible toxin—whether or not it is a chemical poison contained in the putrefactive stool.

We propose from now on to investigate in each case the abnormal chemical elements in the stool with reference to the blood-pressure findings and the kidney retention; and while still feeling that the problem of each case is an individual one, we are hoping that some useful suggestions for treatment in general may be derived from our further work.

The laboratory work was done in the laboratory of the Woman's Hospital of Philadelphia, under the direction of Dr. Berta O. Meine, director of the laboratory.

TWO CASES OF GAUCHER'S DISEASE IN ADULTS: A STUDY OF THE HISTOPATHOLOGY, BIOLOGY AND CHEMICAL FINDINGS.

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UP to the year 1916 only nineteen cases of Gaucher's disease had been reported in which the diagnosis was established by histological examination. An abstract of these cases may be found in a paper on the subject by Mandlebaum and Downey in the *Folia Hematologica*, February, 1916. Since that time the available literature reveals but two authentic cases. The first, reported by Dr. Frank A. Evans, May, 1916, occurred in a boy four years and eleven months of age with a history of splenic enlargement beginning at the age of two years, accompanied by frequent attacks of epistaxis. The histological examination of the spleen and other hemopoietic organs is typical of Gaucher's disease. The second case was described by Dr. Mark S. Reuben, January, 1918. The patient, a boy, aged two years, presented the clinical picture of Gaucher's disease, and an examination of the splenic pulp removed by aspiration revealed the characteristic cells. As a rule, clinicians are opposed to probatory puncture in cases of splenic hypertrophy on account of the danger of hemorrhage, but the diagnosis in suspected cases of Gaucher's disease may always be established if the typical cells are found in the aspirated fluid. This diagnostic procedure was employed for the first time in Gaucher's disease by Bernstein who found the characteristic cells just before splenectomy, the diagnosis being corroborated subsequently by histological examination of the spleen.

The cases reported by Knox, Wahl and Schmeisser in January,

1916, as Gaucher's disease, have no resemblance whatever to that disease and should not have been classified as such. The reasons for excluding these cases from the group under consideration have been published by Downey and the writer. Two cases of splenic hypertrophy occurring in sisters, five and seven years of age, respectively, were reported in March, 1917, by De Lange and Schippers as probable instances of Gaucher's disease, despite the fact that the pathological examination of both spleens removed at operation showed a total absence of the large cells and other characteristic features of that disease. One year later the authors again described the same cases, stating frankly that their original interpretation was incorrect and also admitting their inability to classify the cases.[1]

On account of the infrequency of Gaucher's disease and the uncertainty in the minds of some authors regarding its pathology a further attempt to establish the disease on a firm anatomical basis will be made. In the following report of two cases recently observed and studied, some disputed questions relating to the histogenesis of the large cells found in the hemopoietic organs will be discussed, also the chemical nature of the substance present in these cells.

The clinical and diagnostic features of the disease have been described so often in previous papers that it appears unnecessary to present them in detail at this time, excepting to state that the disease usually begins in infancy or childhood and is characterized by a progressive enlargement of the spleen and subsequently of the liver, a discoloration of the skin of the exposed parts of the body, a peculiar thickening of the conjunctivæ, a tendency to hemorrhages, such as epistaxis or bleeding from the gums, and a definite leukopenia. The superficial lymph nodes are not enlarged, jaundice does not occur and ascites is rare. The disease is distinctly chronic and terminates as the result of a complicating affection. The organs involved are the spleen, liver, lymph nodes and bone-marrow, the distinctive feature being the presence in each of these organs of large cells showing a peculiar type of cytoplasm not exactly duplicated in any other pathologic condition.

Case I.—The patient, a married woman, aged forty-one years, a native of Austria, was admitted to the Mount Sinai Hospital, service of Dr. Morris Manges,[2] November 16, 1915. The family history is negative; no brothers or sisters had any similar disease. The patient is the mother of three children. An operation had been performed at the Presbyterian Hospital in August, 1908, for an abscess of the anterior abdominal wall just below the umbilicus. At that time the spleen, which had been enlarged since an attack of

[1] A discussion of alleged cases of Gaucher's disease reported prior to 1913 and not substantiated by microscopic examination may be found in the paper by Brill and Mandlebaum.

[2] To Dr. Manges and to Dr. Lilienthal, who subsequently operated upon the patient, I am greatly indebted for the privilege of using their clinical records.

malaria in her sixth year, extended from below the tip of the tenth rib on the left side to 4.5 cm. to the right of the umbilicus, and seemed to descend into the pelvis. The surface was smooth and hard; the left border could not be determined. Both legs were covered with black and bluish spots, the patient was poorly nourished and anemic and the temperature occasionally rose to 102°. Blood examination at this time showed 3,200,000 red cells, 2000 leukocytes, hemoglobin, 80 per cent. A later count showed 5000 leukocytes, polymorphonuclears 53 per cent., lymphocytes 47 per cent., hemoglobin 50 per cent. Polychromatophilia was noted and six normoblasts and one megaloblast were seen in a count of 300 leukocytes. The patient was discharged, after five weeks, with the diagnosis of chronic interstitial splenitis.

On admission to Mount Sinai Hospital the patient complained of pain in the left hypochondrium and precordial region, cough, night-sweats, fever of four weeks' duration and blood-tinged sputum for one day. She had lost more than twenty pounds in weight in the course of ten years. The physical examination revealed, in addition to systolic heart murmurs at the apex and over the aortic area, an enormously enlarged and movable spleen reaching into the pelvis. The hand can be placed between the spleen and the costal margin and a notch felt high up. The edge is rounded, the surface smooth; no tenderness. The liver extends from the fifth intercostal space obliquely downward into the right iliac fossa; the edge is thin and sharp, the surface smooth, hard and tender. A pale brownish discoloration of the skin of the face is noted, especially on the forehead; the entire abdomen shows a brown pigmentation, also the lower extremities. In some places, chiefly above the malleoli, the color is brownish black, and on the thighs numerous rounded spots, brown in color and one-half inch in diameter, are seen. Some of the lesions on the legs are evidently the result of hemorrhagic pustules. The superficial lymph nodes are not appreciably enlarged, but a few nodes can be felt in both axillary regions. There is no thickening of the conjunctiva, but a few minute petechiæ seen in both eyes disappeared after four days. For a few days a positive reaction for blood was obtained in the semifluid stools. At this time the hemoglobin was 54 per cent.; red cells, 2,720,000; leukocytes, 2600; polymorphonuclears, 58 per cent.; lymphocytes, 38 per cent.; mononuclears, 4 per cent.; normoblasts, 4 per cent. Subsequently 5 megaloblasts were seen in making a count of 100 leukocytes and poikilocytosis and polychromatophilia noted; one month later myelocytes, 5 per cent., were counted. An examination of the blood for total cholesterin showed 0.11 per cent. The Wassermann reaction was negative. At this time the patient had a severe epistaxis and several attacks followed during the next week. Bone tenderness over the sternum and ribs was also noted. On January 30, 1916, the hemoglobin was 48 per cent.; red cells, 2,688,000;

leukocytes, 1400. The general condition remained about the same and the patient left the hospital a week later. The discharge diagnosis made by Dr. Manges was: "Splenomegaly, Gaucher type."

The patient was readmitted on March 2, 1916, complaining of dragging pains in both legs. The physical examination shows marked pulsation in the suprasternal notch, mitral and aortic murmurs, a huge spleen and liver, intense skin pigmentation and palpable lymph nodes in both inguinal regions and axillæ. The blood examination shows hemoglobin, 60 per cent.; red cells, 4,720,000; leukocytes, 2800; polymorphonuclears, 34 per cent.; lymphocytes, 60 per cent.; mononuclears, 6 per cent. Anisocytosis, poikilocytosis and basophilic stippling are noted.

On March 14 a lymph node was excised from the right axilla and submitted to me for histological examination. The report was: "Chronic fibrosis. A few large reticular phagocytic cells filled with pigment are present. These have a similarity as far as shape and size are concerned to the large cells found in Gaucher's disease. A positive diagnosis cannot be made. The axillary nodes in the reported cases of Gaucher's disease frequently contain but few large characteristic cells." The blood at this time showed a total cholesterin of 0.0875 per cent.[3] The patient refused to be operated upon and left the hospital on April 6, 1916.

She returned to the hospital May 1, 1916, with no pronounced changes in her general condition, and a splenectomy was performed by Dr. Howard Lilienthal on May 29, 1916. A twelve-inch longitudinal incision was made from one inch below the xiphoid to one and one-half inches above the os pubis and a six-inch oblique incision running into the left hypochondriac region at an angle of 75 degrees from the first incision. The spleen occupied the entire left side of the abdomen and part of the right, covering the left lobe of the liver and a portion of the right lobe. The liver was markedly ptosed so that its lower border occupied part of the pelvis. The spleen was easily removed, the entire operation lasting thirty-seven minutes. Immediately afterward a transfusion was performed, the patient receiving 400 c.c. of blood. The postoperative history was uneventful and the patient was out of bed on the ninth day. On the day of operation the blood showed hemoglobin, 55 per cent.; red cells, 2,200,000; leukocytes, 12,000; polymorphonuclears, 62 per cent.; lymphocytes, 36 per cent.; mononuclears, 2 per cent. After transfusion the hemoglobin was 60 per cent.; red cells, 2,420,000; leuko-

[3] The cholesterin content of the blood in many affections of the spleen or liver, especially when accompanied by non-obstructive icterus, such as Banti's disease, pernicious anemia and some forms of splenomegaly with blood changes, is either normal, or decidedly less than normal, in amount. Such is the case in Gaucher's disease. After splenectomy the cholesterin content is always elevated for a certain period, but returns slowly to normal. No particular clinical value can be attached to these findings in Gaucher's disease, on account of the limited number of observations.

cytes, 13,600; polymorphonuclears, 90 per cent.; lymphocytes, 10 per cent.; many normoblasts and megaloblasts. The blood picture was practically unchanged while the patient remained in the hospital and a moderate leukocytosis of from 7000 to 21,000 persisted, with a fairly normal ratio of lymphocytes to polymorphonuclears. The patient gained thirteen pounds in weight and was discharged on July 4, 1916.

HISTOLOGICAL EXAMINATION. The spleen directly after removal weighs 4250 grams (nine pounds six ounces) and measures 38 cm. in the long axis; width at upper pole 16 cm., at lower pole 21 cm., average thickness 9 cm. The general appearance is that of an

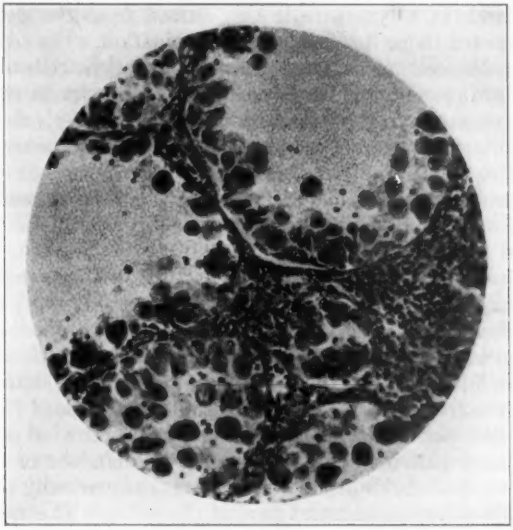

FIG. 1.—Section of spleen. In upper field are two dilated venous sinuses containing large cells and red blood cells. Alveoli filled with large cells are seen below, also collections of normal pulp cells. × 400.

enormously hypertrophied spleen with a well-marked notch. The large vessels are greatly dilated but appear normal otherwise. One small lymph node is seen at the hilus. The surface is dark purplish in color, but a cut section shows a somewhat brownish hue. Very minute yellowish dots are seen on the cut surface, also small hemorrhagic areas with yellowish markings. These areas protrude slightly above the cut surface and have an average diameter of 0.5 cm. A few red infarcts of small size are also noted. There is no apparent increase of connective tissue. Stained smears made from the freshly cut surface show numerous large, multinucleated cells characteristic of Gaucher's disease.

Frozen sections were made at once from the fresh spleen and stained with Sudan III and Nile blue, but no trace of fat or lipoid substances could be found. Examination of frozen sections with the polariscope failed to show any anisotropic bodies.

Blocks of tissue were preserved in alcohol, Zenker's solution, formalin and Helly's fluid, and the sections stained by a large variety of methods. The sections show the typical picture so often described in the genuine cases of Gaucher's disease. The pulp is almost entirely replaced by large, round or oval, alveolar spaces containing the characteristic cells. Many of these spaces are dilated venous sinuses bounded by a narrow band of connective tissue and partially lined with flattened endothelial cells. In addition to the large cells one also sees numerous red blood cells. Other alveoli contain only large cells and are bounded by delicate connective-tissue septa with no endothelial lining (Fig. 1). Many adjoining sinuses communicate with each other and in some situations the wall is broken and the sinus communicates directly with the pulp. The Malpighian bodies are diminished in number and those present are moderately hypertrophied. Small collections of normal pulp cells are crowded between the dilated sinuses. A small amount of bright yellow pigment is found in the sections. This is in form of minute crystals lying free or contained in small reticular cells. The pigment gives a positive reaction for iron. There is no positive evidence in these sections that the Gaucher cells are phagocytic for erythrocytes. A few multinuclear cells resembling megakaryocytes are seen here and there.

Although an examination for the presence of fat or lipoids had been made on frozen sections of fresh spleen with a negative result, as mentioned above, additional polariscopic and microchemical tests were made on frozen sections of the tissue fixed in formalin. These tests were uniformly negative, confirming the statement repeatedly made that lipoid substances cannot be found in the Gaucher cells by microchemical methods.

Sections of the small lymph node found at the hilus of the spleen present the typical picture described in this disease and show a moderately advanced involvement. Large cells are seen in considerable number, but the lymph-adenoid tissue is only partially replaced by these cells. The individual follicles are still clearly outlined, principally those near the cortex, and no marked activity is seen in the germinal centers. The sinuses are moderately dilated and contain lymphocytes, erythrocytes and pigmented cells. The pigment is both crystalline and amorphous in character, of a brownish-yellow color and is seen along the trabeculæ, in the fixed cells of the reticulum and in the sinuses. Only a small number of pigment granules give a positive reaction for iron, the crystalline form being negative.

From this brief description of the spleen and lymph node it may

be seen that the histopathology is typical of Gaucher's disease. In order to avoid repetition the structural details of the large cells will be described later in connection with a consideration of their origin and nature.[4]

CASE II.—The patient, male, aged thirty-seven years, a native of this country, was admitted to Mount Sinai Hospital, service of Dr. A. A. Berg,[5] January 14, 1918. Both parents and several brothers died of causes unknown to the patient; one brother alive and well. At the age of twenty-five he consulted a physician for diffuse abdominal pain and was told that "something was beginning to grow" in his abdomen. The pain ceased soon afterward, and he experienced no further abdominal symptoms for ten years. Then he noticed a gradual enlargement of the abdomen, accompanied by a dragging sensation. The only other complaint was frequent attacks of epistaxis, at times profuse in character. Four months before admission he began to have sharp pains in the left hypochondrium, radiating to the shoulder and extending over the entire abdomen. The heavy, dragging sensation persisted. No history of fever or loss of weight.

The physical examination on admission reveals a well-developed though slightly emaciated man with a markedly protuberant abdomen. The spleen is greatly hypertrophied; the lower pole felt midway between the umbilicus and the left anterior superior spine. A distinct notch is felt a few inches below the costal margin, the edge is sharp, the surface smooth, not tender, and the organ moves freely with respiration. The liver is not apparently enlarged and cannot be palpated. A distinct fluid wave is elicited in the abdomen. The skin of the face is somewhat dark in color and many brownish colored patches and scars are seen on the legs. The superficial lymph nodes are not distinctly enlarged, but a few soft nodes are palpable in the axillæ. A distinct conjunctival thickening is present in each eye on both sides of the cornea. The Wassermann reaction is negative. The blood on examination shows hemoglobin, 35 per cent.; red cells, 3,500,000; leukocytes, 9000; polymorphonuclears, 52 per cent.; lymphocytes, 46 per cent.; mononuclears, 2 per cent. Poikilocytosis and anisocytosis are noted, but no nucleated erythro-

[4] The patient again entered the hospital on April 5, 1918 (two years after the splenectomy), complaining of pain in the right thigh and loss in weight. Her general condition had improved after the operation, the epistaxis had not returned, the pain in the legs disappeared and she gained in weight. On admission it was noted that the skin pigmentation was less prominent and of lighter color. The cervical, axillary and inguinal lymph nodes are small but palpable. The liver extends from the upper border of the fifth rib to 15 cm. below the costal margin; surface and edge slightly irregular. Some tenderness of long bones and sternum noted. Hemoglobin 68 per cent., red cells 3,600,000, leukocytes 7500, polymorphonuclears 55 per cent., lymphocytes 36 per cent., mononuclears 6 per cent., transitionals 2 per cent., eosinophiles 1 per cent., a few normoblasts. Total cholesterin 0.194 per cent.

[5] I am deeply indebted to Dr. Berg for his kindness in permitting me to study this case and for the use of the clinical data.

cytes are seen. Examination for total cholesterin shows 0.108 per cent.

Both Dr. Brill and the writer, who were asked to examine the patient, concurred in the diagnosis of Gaucher's disease.

Five days after admission a splenectomy was performed by Dr. Berg. A long transverse incision was made parallel to the lower edge of the ribs from the midline downward and outward as far as the costovertebral angle, and upon opening the abdomen more than a liter of bloody fluid escaped. Many dense adhesions were found between the spleen and omentum, prolonging the time of operation. Drainage of the wound was made. A blood transfusion of 600 c.c. was then performed and the patient reacted satisfactorily. On the following day the blood showed hemoglobin, 50 per cent.; red cells, 3,776,000; leukocytes, 28,800; polymorphonuclears, 80 per cent.; lymphocytes, 17 per cent.; mononuclears, 3 per cent.; many normoblasts but no megaloblasts. Two days later the blood picture was practically the same but the leukocyte count fell to 23,600. For ten days the patient's condition remained satisfactory, then the temperature rose to 105° following a chill, and a considerable amount of serous fluid escaped from the drainage opening. The patient's condition from this time became steadily worse, and two days later the original wound opened spontaneously. This was again sutured, but the patient continued to have high temperature, and died February 6, 1918. Examination of blood for total cholesterin four days before death showed 0.132 per cent.

Histological Examination. The spleen immediately after removal weighs 3500 grams (seven pounds eleven ounces) and measures 25 x 18 x 12.5 cm. The general configuration of the organ is retained. There are four notches on the anterior border and two on the posterior border. A number of large omental adhesions are seen in the neighborhood of the hilus. The surface is smooth but marked by numerous small, globular elevations which project slightly above the surface. These correspond to small hemorrhagic areas seen upon cross-section of the organ. The color on section is grayish or purplish brown, the consistency firm, the surface rather smooth but dotted with innumerable semitranslucent areas measuring about 1 mm. in diameter. A number of rounded hemorrhagic areas with central necrosis are seen on the cut surface, varying from 1 to 4 cm. in diameter. The Malpighian bodies cannot be recognized. At the hilus a few dark red lymph nodes are seen. These measure from 0.5 to 2 cm. in diameter.

Smears made from a freshly cut surface show many characteristic large cells with multiple nuclei. Frozen sections were made from the fresh spleen and stained with Sudan III and Nile blue, but no lipoid substances or fat could be found. Polariscopic examination for double refracting substances was also negative. The histological picture as seen in paraffin sections is almost identical

with that described in the previous case, and therefore requires no detailed description. Microchemical tests for fat or lipoids made on frozen sections of the spleen fixed in formalin were uniformly negative. A small amount of pigment is seen in the trabeculæ and in the walls of the larger bloodvessels.

Postmortem Examination. This was performed five hours after death by Dr. William Thalhimer. The body is that of a poorly nourished man, with a peculiar brownish color of the skin. Numerous dark brown, circular areas of pigmentation are seen on both legs. A long incision in the left hypochondrium extends from below the free border of the ribs in the median line downward and outward to the costovertebral angle.

Heart: Normal.

Lungs: Normal in size and appearance; crepitation throughout; several firm, dark areas 1 to 2 cm. in size just below the pleura.

Thymus: Fatty remains only are present.

Tracheobronchial lymph nodes: Considerably enlarged, soft, pinkish color on section, succulent.

Abdomen: About 500 c.c. thin, bloody fluid present. Peritoneal surfaces smooth and glistening everywhere. The splenic vessels are ligated with heavy silk and are in good condition. A thin layer of fibrin is seen in this region, but no other exudate is found.

Liver: Weight, 2040 grams; right lobe measures 23 x 19 x 10.5 cm.; left lobe, 17 x 14 x 4.5 cm. The surface presents a peculiar grayish-brown color; slightly increased resistance to knife on section; cut surface is pale, succulent and broken up into small islands by increased connective tissue. Nearly all of the radicals of the portal vein are completely filled with slightly adherent mixed thrombi, red and white. The portal vein is completely filled by a recent dark red, slightly mixed, adherent thrombus, lamellated in places and very soft. The thrombus extends up the portal vein into all its radicals and down into the splenic vein, which is completely filled as far as its ligated end. It extends down as far as the openings of the large mesenteric veins into the portal, but does not extend into the mesenteric veins proper. The gall-bladder is somewhat enlarged, densely adherent to the transverse mesocolon, causing a slight constriction of the duodenum and contains one small rounded calculus. The bile ducts appear normal.

Kidneys: Normal size, capsules not adherent, surface pale and smooth; on section, somewhat cloudy.

Adrenals: Slightly smaller than normal; medulla, dark brown in color.

Esophagus: Normal.

Stomach: Enormously distended with gas. The veins contain no thrombi; mucosa, hemorrhagic in places.

Intestines: Mucosa of duodenum studded with small, bright red, hemorrhagic areas; same condition present in entire length of small

and large intestine; mucosa slightly edematous; lymphoid follicles and Peyer's patches normal in size and appearance.

Abdominal lymph nodes: Mesenteric and retroperitoneal lymph nodes enlarged to about twice the normal size; soft, succulent, pinkish color on section. A small calcareous deposit is seen in one mesenteric node.

Pancreas: Normal.

Bone marrow of vertebræ: Dark red in color, soft in consistency.

HISTOLOGICAL EXAMINATION. Blocks of all the organs removed were fixed in a large variety of fluids and paraffin sections were studied.

FIG. 2.—Section of liver. Large cells in the inte lobular connective-tissue spaces on the right. Columns of normal liver cells on the left, also large cells in the sinusoids. × 400.

Liver: Although this organ is not enlarged, contrary to the rule in cases of Gaucher's disease, the picture is typical. With low magnification one sees an enormous increase of interstitial connective tissue, giving the appearance of a fibrosis. With higher power, large masses of Gaucher cells are seen in the meshes of the interstitial tissue and also invading the peripheral portions of the lobules (Fig. 2). The large cells are also found in many of the sinusoids, but the stellate cells of Kupffer are not involved in the process. The individual hepatic cells are quite normal. A few masses of brownish pigment are seen here and there, especially in and near the walls of some of the larger bloodvessels. The thrombotic process in the

portal vein and its branches shows definite organization with the presence of many young fibroblasts. The fatal termination may be attributed, without question, to the extensive portal thrombosis.

In some of the livers that we have examined the recognition of the characteristic large cells is a matter of some difficulty, and it has been frequently necessary to employ special stains for their detection. In this case, however, the individual cells are quickly and easily detected by the usual staining methods, even in those places where a large number of the cells are compressed into extensive fused masses.

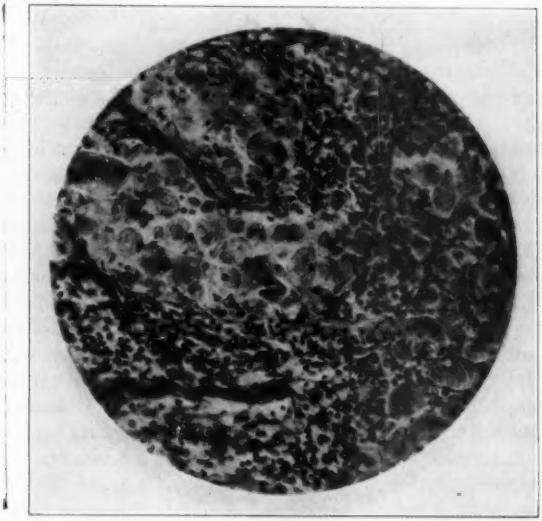

FIG. 3.—Section of retroperitoneal lymph node showing several alveolar spaces filled with large cells, also areas of normal pulp cells. × 400.

Lymph Nodes: The degree of involvement varies in the different regional groups. The mesenteric and retroperitoneal nodes as well as the nodes at the hilus of the spleen and along the splenic vein show an advanced process, the nodes at the hilus of the liver a slighter degree of involvement, while the tracheobronchial and esophageal nodes present only an early stage. The nodes in which the process is far advanced show an almost complete disappearance of normal lymphadenoid structure, the entire node being replaced by the characteristic large cells (Fig. 3). Here and there in these nodes the remnants of a follicle may be seen, usually in the cortical zone. In one of the nodes at the hilus of the spleen, however, one portion was quite normal in appearance, while the remaining part showed a high degree of involvement, the cells here being fused

into long strands and large syncytial masses. In some of the retroperitoneal nodes the cells are of enormous size, and in one of these cells twenty-one nuclei were seen. The largest number hitherto recorded in a single cell is thirteen. In none of the nodes examined do the germinal centers show any abnormal activity, such as is frequently noted in cases occurring in infants or children. The quantity of pigment is variable, a large amount being seen in the esophageal and tracheobronchial nodes, in the nodes at the hilus of the spleen and along the splenic vein, and only a few granules in the mesenteric and retroperitoneal nodes. A positive iron reaction is obtained in some of the pigment only.

Bone-marrow: The large cells are seen singly and in extensive groups and present the general characteristics noted in the other hemopoietic organs. No pigment is seen.

Other Organs: A careful microscopic examination was made of the heart, aorta, lungs, thymus, kidneys, adrenals, pancreas and intestines. No large cells could be found in any of these organs, corroborating the findings in all previous authentic cases.

The lymph-adenoid tissue of the small intestine was found to be normal, but some pigmentation of the muscle fibers was seen. This observation has been made in other cases. The thoracic and abdominal aorta were carefully studied but no cellular changes were found.

The second case, therefore, is a typical instance of Gaucher's disease, conforming in its pathological aspects with eleven other cases which the author has had the opportunity of studying histologically.

The Presence of Large Cells in Other Conditions. Before proceeding to a description of the typical cells of Gaucher's disease a few remarks on other conditions accompanied by the presence of "large cells" may result in a clearer conception of the entire problem.[6]

It has been shown by numerous investigators that certain groups of cells, notably the reticular cells of the hemopoietic organs, are susceptible to the effects of various agents, bacterial, toxic, metabolic or chemical, the type of reaction depending in each case upon the nature of the irritant concerned. Thus, Mallory, in 1898, described certain cellular changes in the spleen, lymph nodes, bone-marrow and liver in cases of typhoid fever. He called the cells involved in this process "endothelial leukocytes" and recognized the biological importance of these cells reacting as a group to a definite toxin.

The tubercle bacillus is another agent capable of producing cellular

[6] The author may be pardoned in the following portion of the paper for referring rather extensively to the article on Gaucher's disease by Mandlebaum and Downey, inasmuch as no copies of the Folia Hematologica have been received in this country since the article was published.

reactions in this group of cells, especially in the spleen and lymph nodes. The cellular hyperplasia in the spleen in splenomegaly due to tuberculosis may be a prominent histological feature. In fact, two cases of this nature have been incorrectly classified in the literature as instances of Gaucher's disease, and the material from two additional cases, in which the diagnosis of Gaucher's disease had been suggested, has recently been submitted to the author for study. It should be mentioned here, however, that two typical cases of Gaucher's disease have been reported in which foci of tuberculosis have been noted (Schlagenhaufer, Erdmann and Moorhead). These two cases conform in all respects to the other authentic cases unaccompanied by tuberculosis, and the tuberculosis here is evidently a superimposed process.

The injection of carmine or acid colloidal dyes into animals produces changes in the same specific group of cells, as shown by Kiyono and others, the cells having received different names by the various authors who have worked on the subject. These cells, the "histiocytes" of Kiyono and Aschoff, the "pyrrhol cells" of Goldman, the "resting wandering cells" of Tschaschin, the "macrophages" of Evans, are the fixed cells of the reticulum of the hemopoietic organs, the free cells derived from the reticulum, the Kupffer stellate cells of the liver, the clasmatocytes of loose connective tissue and the lymphoid cells of the milky patches of the omentum. The reaction of these cells in vitally stained animals has been fully described in the literature. This specific group of cells has been termed "endothelialer Stoffwechselapparat" by Landau and Aschoff.

The cells just mentioned are practically identical with the cells involved in storing lipoids in animals fed upon fatty substances or cholesterin, as shown by Anitschkow, and a striking resemblance to the lesions found in Gaucher's disease has been noted in these animals. The similarity is so marked, in fact, that Aschoff called the condition "pseudo-Gaucher." Anitschkow calls all the cells involved in this process "cholesterinesterphagocyten."

Experimental bacteremia, as shown by various authors, is often followed by marked activity of the reticular cells, as well as phagocytosis, the extent of the process and the type of cell involved depending upon the organism employed and the conditions of the experiment.

In 1912 Schultze called attention to important cellular changes in a case of diabetes associated with lipoidemia. In this case and in two cases of a similar nature subsequently published by Lutz the cellular reactions were limited to the spleen, but Lutz described areas of cholesterin cells in the aorta of his first case, recalling the lesion produced in the animal-feeding experiments of Anitschkow. In a case of the same type reported by Williams and Dresbach large cells were found in the liver and lymph nodes, in addition to the cellular hyperplasia in the spleen, and certain striking changes were seen in the adrenals suggesting those described by Antischkow in

his animal experiments. Following Schultze's publication, in which he noted the resemblance to Gaucher's disease but erred in stating that the large cells of Gaucher's disease undoubtedly contain lipoid substances, the subject has been somewhat confused and some authors have reported as instances of Gaucher's disease, other morbid processes accompanied by the presence of "large cells."

From what has been said above it is apparent that various factors may be concerned in the production of large cells; also, on purely biological grounds, that the histopathology and microchemical features of these cells must depend in each instance upon the etiological factor concerned. And it is also evident that all diseases or conditions in which large cells are found are not cases of Gaucher's disease. In cases of diabetes associated with lipoidemia, for instance, or in animals fed upon fatty substances, the large cells present histological and chemical characteristics never seen in Gaucher's disease or in the cells concerned in vital staining, one of the most striking features in the diabetic cases and in the animal experiments being the presence of anisotropic bodies and lipoid substances in the large cells. These substances are never found in true cases of Gaucher's disease, as we have repeatedly shown.

An improper appreciation of the facts and observations just cited is one of the reasons for some of the errors in the diagnosis of Gaucher's disease and the limited number of detailed histological and biological studies of all of the above conditions is in part responsible for the controversies regarding the origin and nature of the reacting cells. The clinical factors and the histopathology of Gaucher's disease are characteristic and well-defined, and this disease should never be confused with other conditions. In our previous article we said that "the description of a single case may readily serve, with minor variations, as the basis for all the genuine cases reported," and this statement may with propriety be repeated again.

The Large Cells of Gaucher's Disease. Following the first contribution to the subject in 1882 by Gaucher, considerable controversy has arisen in regard to the large cells, the chief discussion revolving about the question as to whether the cells are derived from endothelium or reticulum. The authors who have written upon the subject have been about equally divided on this point, and some have stated that the cells may originate from both sources. It is beyond the scope of this paper to present in detail all of the arguments brought forward by the various writers to prove their contentions, but the recent investigation of Mandlebaum and Downey seems to permit an accurate determination of the origin of the cells.

The large cells show considerable variation in size, the average diameter being from 20 μ to 40 μ, but occasionally cells of huge size are seen, three or four times as large as the average. They are round or oval in shape when more or less isolated, but when large compressed areas are found the cells are usually fused into long strands

or united as syncytial masses. The large cells show a strong affinity for acid stains which bring out clearly a network of fine fibrils running in a wavy, parallel course in the direction of the longitudinal axis of the cell. This gives to the cell its streaked or wrinkled appearance, but when the cell has been cut transversely to the main direction of the fibrils the cytoplasm appears granular or stippled. In many of the cells one sees irregularly shaped or elongated, colorless areas bounded by the fibrils which have been crowded apart. The shape of these colorless spaces is an important point of distinction between the Gaucher cells and the cells seen in the diabetic lipoidemia cases or in the animal-feeding experiments, for in the latter two conditions the colorless spaces or vacuoles are rounded. Furthermore, the characteristic streaked or wrinkled appearance of the Gaucher cells and their tendency toward fusion or the production of long bands are never seen in the lipoid cases; finally, multinuclear cells, common to Gaucher's disease, are never encountered in the diabetic lipoidemia cases. In addition to the cells just described, which are typical for the disease, other cells are seen with a more homogeneous cytoplasm and little or no evidence of fibrils or colorless spaces. As previously stated, the Gaucher cells never contain fat or lipoids, the microchemical and polariscopic tests for these substances being constantly negative. Glycogen, amyloid and oxydase are also absent and the cells remain unchanged after treatment with potassium hydrate or strong acids. Alcohol, ether, chloroform, aceton and xylol have no solvent action on the cytoplasm of the large cells, for there is no change in the staining qualities after the use of these reagents, excepting that the fibrillar structure is rendered more prominent and the cells appear somewhat shrunken.

The nuclei, as a rule, are irregular in shape, small in proportion to the size of the cell, and eccentrically placed. Many contain a considerable amount of chromatin and appear dark. Cells with two or more nuclei are common and as many as twenty-one were counted in a single cell in the second case just reported. The cells with homogeneous cytoplasm frequently contain nuclei which are larger than those just described, round or oval in shape, with one to three nucleoli. Other cells may show small, dark, pyknotic nuclei, apparently degenerating forms. Cell division by amitosis has been described by De Jong and Van Heukelom and by the writer.

The amount of pigment in the large cells is variable. As a rule it is more abundant in the large cells of the lymph nodes than in those of the spleen or liver. A large amount is usually found when extensive hemorrhagic areas are present. While most of the pigment is located in the fixed cells of the reticulum and in the reticular macrophages a certain amount may be found in the characteristic large cells. Some cells may contain so many pigment particles that the character of the cell cannot be determined. The pigment is bright yellow or brownish in color and may occur in the form of

crystals or as rounded, dense masses. When seen in the latter form it usually gives a positive reaction for iron. A certain number of phagocytic cells are seen containing erythrocytes, but it is impossible to say definitely whether these are true Gaucher cells. In a former paper the author stated that the large cells were phagocytic for erythrocytes, agreeing on this point with the claim made by Risel. In the subsequent studies made with Downey, however, this question could not be decided positively. A point in favor of the phagocytic character of the large cells is the intense blue color in some of the cells when the staining reaction for iron is made. This may be explained by a transformation in the cells of the hemoglobin products after phagocytosis into a soluble and diffusible iron compound.

Our observations on the histogenesis of the large cells were made chiefly in a study of the lymph nodes. These show different degrees of involvement in the various regional groups, and the process can be studied here with greater accuracy than in the spleen in which the lesion is usually so far advanced that the early changes may be more or less obscured.

In lymph nodes showing an early stage of involvement the reticulum, excepting that which forms the walls of the sinuses, is hypertrophied. In these nodes, as well as in the nodes with a more advanced process, the reticular cells of the sinus walls always remain normal and no large cells are seen within the lymph sinuses. The follicles are surrounded by a thick layer of cellular reticulum and the germinal centers contain large, phagocytic reticular cells. Isolated Gaucher cells are found here and there, and long bands of Gaucher tissue are seen directly continuous with the surrounding reticulum.

In the nodes in which the involvement is far advanced the follicles or remnants of follicles are always surrounded by a ring or wall of large cells and in the center of the follicles large cells are seen. The process begins in a small group of large cells in the germinal center or at the periphery of the follicle. These cells spread until the follicle is almost surrounded, and the cells also spread outward from the germinal center In this way the follicle is gradually replaced by Gaucher cells and the lymphocytes gradually disappear. The significant fact, as shown by Downey, is that the Gaucher tissue occurs in those regions in which the reticulum shows distinct evidence of hypertrophy. The cellular reticulum in normal lymph nodes is very abundant in the germinal centers and a thick layer may surround the follicle. In both regions it changes its character very readily whenever the node is placed under abnormal conditions of any kind. Downey has shown by tracing strands of normal reticulum that they finally loosen up and assume the same identical structure as the Gaucher cells, proving beyond question that the Gaucher cell is merely modified cellular reticulum, that is, modified by the storage of some foreign substance taken up. This accounts for the apparent fusion of Gaucher cells into syncytial masses and

for the long cells, and also for a reduction in the amount of normal reticulum within the masses of Gaucher cells (Fig. 4). It must be noted that the disappearance of normal reticulum applies to its cells, for the fibers may be present in normal numbers, forming a close network around the Gaucher cells. Most of the reticular fibers are merely in contact with the surface of the cells, but some cells are found which contain fibers within their cytoplasm, as noted by Downey. This is also strong evidence that the Gaucher cells are modified reticular cells. During the progress of the disease most of the cells become detached from the fibers and become isolated cells. This often occurs in normal nodes and the reticular cells

FIG. 4.—Section of lymph node at hilus of spleen. Near the upper border is a strand of normal reticulum which spreads out, assuming the structure of the cytoplasm of the large cells. The character of the Gaucher tissue is seen in the syncytial masses. A sinus wall with normal "endothelium" is seen at the upper border. Camera lucida drawing, Zeiss apochrom. obj. 4 mm., ocular 6.

become free wandering cells. The reticular fibers may also disappear, probably owing to the fact that they have become separated from their cells.

The so-called "endothelium" which lines the sinuses is absolutely normal. The present view is that this "endothelium" is really part of the general reticulum. The cells here in normal nodes are very active as phagocytes, often separate from their fibers and enter the sinuses as free cells (endothelial leukocytes of Mallory). Some reaction might be expected in Gaucher's disease in this reticulum, but our study shows that this reticulum is always normal no matter how advanced the process. The Gaucher cells, therefore, are

certainly not of "endothelial" origin, and our material shows no evidence for the transformation of the reticulum bordering any of the sinuses of the lymph nodes into Gaucher tissue.

It is difficult to say why the reticulum of the sinuses should show no reaction in Gaucher's disease, but other analogous conditions are also difficult to explain. In the Anitschkow animals the feeding of cholesterin caused the appearance of lipoid-containing cells in the intima of the aorta, but the endothelium was unaffected. Similarly, in vital staining the reticulum forming the sinus wall is very active and reticular cells in other parts of the node show great avidity for the dye particles, while those in the germinal centers take up little or none of the dye. In Gaucher's disease most of the reticulum may become transformed into the characteristic tissue, but many normal reticular cells not affected by the process may be found. Mechanical conditions may possibly play an important part and the free circulation of lymph through the sinuses may be a factor in keeping the cells normal in Gaucher's disease, while in the vitally stained animals the dye is brought into the node through the lymph vessels and comes into direct contact with the reticulum of the sinuses. If the substance in the cases of Gaucher's disease is brought to them through the lymph stream one would expect the reticulum of the sinuses to react as it does in the dye animals and assume the character of Gaucher tissue. The fact that it does not react in this way is an argument in favor of the view that the substance is produced by the reticular cells and stored within their cytoplasm. On the other hand, one must not overlook the fact that in Anitschkow's animals the lipoids passed between or through the endothelial cells of the aorta and were stored in the cells of the intima, leaving the endothelial cells unchanged. One must also remember that the endothelium of blood and lymph vessels does not show the same avidity in taking up foreign substances as does the reticulum of the lymph sinuses. One cannot draw definite conclusions in regard to the origin of the substance in the Gaucher cells from these examples, for the reactions in experimental lipoidemia and in vitally stained animals are not exactly parallel. A comparison of the reactions of the reticulum in Gaucher's disease with the reactions in vitally stained animals is against the exogenous origin of the substance, while comparison with the lipoidemia cases is, to some extent, in favor of such an origin. Viewing the question from a biological standpoint and also taking into consideration the fact that the cellular reticulum of the hemopoietic system is not a highly specialized tissue, the writer is inclined to the opinion that the substance contained in the large cells is exogenous rather than endogenous in origin.

Downey has noted that the connective-tissue cells of the liver and of the walls of its veins may become transformed into Gaucher cells identical in structure with those of the lymph nodes and spleen. The reticulum lining the sinusoids (Kupffer cells) is not involved in

the process, therefore the origin of the free Gaucher cells within the sinusoids must be accounted for in some other way. That these cells are carried into the liver through the splenic vein seems probable, as the Gaucher cells are frequently seen in the larger branches of the portal vein. There is no evidence for an endothelial origin of the cells in the liver and no evidence that the cells proliferate in the liver after being carried through the splenic vein. It remains uncertain whether the Gaucher tissue of the liver represents modified fibroblasts or reticular cells. According to Rössle and Yoshida, who have described the transformation of reticular tissue to collagenous tissue, it may be assumed that the same cells may produce both reticulum and collagenous fibers and that there may be no fundamental difference between fibroblasts and reticular cells. The parent cell may, therefore, produce a reticular cell, a fibroblast or a Gaucher cell.

From what has been described in the lymph nodes, it is evident that the histogenesis of the large cells in the spleen is the same, but the process in the spleen in all the cases we have examined is too far advanced to permit of the same accurate determination as in the lymph nodes. On account of the direct communication of the sinuses with the surrounding pulp, it seems possible that most of the free Gaucher cells within the sinuses have come from the surrounding pulp and are derived from the reticulum. There is no positive evidence in the spleen, however, that the endothelium of the sinuses does not take part in the formation of the large cells, and the possibility of derivation from this source cannot be denied. The fact that the walls of the dilated sinuses containing Gaucher cells are composed of a dense fibrous tissue, usually without an endothelial lining, is in favor of this view. In the bone-marrow it may be assumed that the Gaucher cells are derived from the reticulum, inasmuch as the marrow contains a reticular framework similar to that of the lymph nodes.

From the foregoing description it may be seen that a definite and characteristic reaction of the reticulum of the hemopoietic system occurs in cases of Gaucher's disease. Although the changes in some of the organs bear a certain resemblance to other conditions, such as the diabetic lipoidemia cases and the reactions in cholesterin-fed animals, a clear distinction may be made histologically and chemically in the character of the large cells, and the claim of practical identity of Gaucher's disease with lipoidemia cases is not justified.[7]

Studies of Lipoids. The subject of lipoid substances in the large cells of Gaucher's disease has now been investigated in 6 cases, 4 children and 2 adults. In 2 of the cases it was possible to use only material fixed in formalin, but in the remaining 4 cases (2 children, 2 adults) fresh material was also employed. In all of these

[7] A critical study of the histopathology of vitally stained animals, diabetic lipoidemia cases and cholesterin-fed animals as compared with Gaucher's disease is given in the paper by Downey and the writer.

cases the observations were made chiefly upon frozen sections of spleen. In 1 case, however (Case II, reported above), studies were also made of the fresh liver and bone-marrow. The chemical and polariscopic tests were uniform in all of the cases, therefore it is unnecessary to specify each case individually.

Frozen sections of fresh spleen stained with Nile blue, Sudan III and Scharlach R are always negative (absence of neutral fat, cholesterin esters, lipoid substances, fatty acids and soaps). Nile blue often shows a faint bluish color of the entire section, but the normal pulp cells hold the stain more than the large cells. The Smith-Dietrich method produces either a very light grayish-blue color or a dirty brown color of the large cells, depending upon the duration of the stain and the amount of differentiation, but no lipoid or myelin substances can be detected. Fischler's method shows a light, diffuse, bluish color in some of the cells, while other adjoining cells remain colorless. No blue-black granules or crystals (glycerin esters, fatty acids or soaps) are found in any of the large cells. Ciaccio's methods show a few isolated spherical bodies of minute size, yellowish orange in color, in some of the cells. These are not more numerous than one might expect in any tissue treated by this method.

Weigert's myelin sheath stain, which, according to Schultze, gave a positive reaction in his case of diabetes, is entirely negative. The large cells show a pale, grayish color, homogeneous in character, but no lipoid substance is seen. These sections were stained with iron-hematoxylin for twenty-four hours, and after differentiation were cleared in benzin as well as in xylol. The Weigert-Van Gieson method as recommended by Schultze is also negative. Some of the latter sections were overstained, decolorized by acid alcohol and cleared in benzin, but the results were constantly negative. Sections treated with osmic acid for twenty-four hours and then exposed to the light for the same length of time are negative. Sections stained with neutral red are also negative, the entire section being faintly red, the large cells holding the color least of all. Sections tested for cholesterin, fats and free fatty acids by the Golodetz method and by Lugol's solution followed by sulphuric acid, 30 per cent., are also negative. With the latter test a brown color appeared, but no change into blue or green after an observation of thirty minutes. Crystals of cholesterin as control for these two methods showed positive reactions in both instances.

Unstained frozen sections examined with the polariscope show no double refracting substances (cholesterin esters, myelin substances). All of the sections stained with Nile blue were also examined with the polariscope, but anisotropic bodies were never seen.

The liver of Case II was examined in the fresh state. Polariscopic examination of frozen unstained sections as well as sections stained with Nile blue are negative for double refracting substances. Sudan III shows a few red droplets in the liver cells here and there (fatty

degeneration), but no reaction in the large cells. Smears made from the fresh bone-marrow in the same case show no anisotropic bodies by polariscopic examination.

Assuming that lipoids might be present combined in a highly complex protein molecule and hence difficult to identify microchemically, an attempt was made to break up this combination by the action of artificial digestive fluids. Thin blocks of formalin-fixed spleen were treated with ammonium hydrate, 2 per cent., for one hour, to neutralize the formalin and then washed in running water for eighteen hours. Frozen sections were made and placed in a solution of pepsin, 0.1 per cent., hydrochloric acid, 0.2 per cent., in an oven at 37° C. Sections were then stained with Nile blue and Sudan III and also examined with the polariscope at intervals up to 100 hours, but no reactions for fat or lipoids could be obtained. The activity of the fluid was evidenced by a slow digestion of the tissue after sixty hours, but a sufficiently large number of the Gaucher cells remained for the tests. Other sections were subjected to the action of trypsin, 0.5 per cent., and sodium bicarbonate, 0.5 per cent., and stained as above at intervals up to fifty hours. The reaction for fat or lipoids was also negative in this series. In both instances the staining qualities of the large cells remained unchanged, showing no fission of the combination in the cells.

A complete chemical analysis was made in 3 cases in order to determine the presence of fats or lipoids, for it was recognized that these substances might be present despite the negative results of microchemical tests. The material employed for this work consisted of 5 grams of spleen fixed in formalin from each of 2 cases occurring in children (Case I and Case II in table) and 100 grams of fresh spleen and an equal amount of formalin-fixed spleen from the male adult case reported in this paper (Case III in Table).[8]

Technic. The material was first dried on a water-bath and for two successive days for three hours each, in a drying oven at 70° C., until a constant weight was reached. The material was then extracted in four times its volume of absolute alcohol at 37° C. It was then filtered and the entire process repeated three times. Extraction in a Soxhlet apparatus with absolute alcohol for ninety-six hours followed. This process was repeated with ether and chloroform each for ninety-six hours. The entire extractives were then mixed, evaporated to a small volume and transferred to a large weighed platinum dish. The material was then evaporated to dryness in the air, placed in a drying oven at 70° C. for three hours and weighed. It was then redissolved in hot absolute alcohol and immediately filtered to eliminate any salts. It was then re-evaporated, re-dried and re-weighed. The process was repeated until a constant weight

[8] It is a great pleasure to thank Dr. M. A. Rothschild for the chemical examination of the two children's spleens and for valuable coöperation throughout the lipoid studies, and Dr. S. Bookman for his kindness in performing the analysis of the adult case and for his keen interest in the entire chemical investigation.

was obtained, thus obtaining the total weight of the extractives. It was then redissolved in 250 c.c., of mixed solvents, ether, absolute alcohol and chloroform. It was then divided into five portions of 50 c.c. each. Two 50 c.c. portions were used for nitrogen determination, employing the Kjeldahl apparatus; 50 c.c. were used for the phosphorus determination, the phosphorus being determined as $Mg_2P_2O_7$; a fourth portion was used for total cholesterin determination, employing the Autenrieth-Funk colorimetric method.

The fatty acids were determined by shaking 50 c.c. of the mixed solvents with sodium hydrate, 10 per cent., in a separating funnel. The watery solution containing the free fatty acids was separated from the mixed solvents, acidified with phosphoric acid and shaken out with ether. It was purified until a constant weight was reached and its acidity determined in terms of stearic acid, using a $\frac{1}{10}$ normal solution of sodium alcoholate and phenolphthalein as an indicator.

The mixture of combined or saturated fatty acids which had been separated from the watery solution was saponified with alcoholic sodium hydrate on an electric bath with a return condenser for six hours. The solution was evaporated until no trace of solvents was present, acidified with an excess of phosphoric acid and extracted with ether. The fatty acids were determined as above and the acidity ascertained in terms of stearic acid.

LIPOID CONTENT OF SPLEENS. TABLE I.

	Case I.	Case II.	Case III.	
	Dried formalinized spleen.			Dried fresh spleen.
	Per cent.	Per cent.	Per cent.	Per cent.
Extractives	34.4	23.47	19.895	27.687
Cholesterin	1.86	1.77	10.151	9.214
Lecithin	14.29	17.2	3.71	3.448
Nitrogen	0.59	0.66	0.503	1.539
Free fatty acids	2.7	1.5	2.804	0.000
Combined fatty acids	9.9	2.7	5.835	19.948

The following figures are obtained from Table I, calculated as percentages of the extractives:

TABLE II.

	Case I.	Case II.	Case III.	
	Dried formalinized spleen.			Dried fresh spleen.
	Per cent.	Per cent.	Per cent.	Per cent.
Extractives	34.4	23.47	19.895	27.687
	Percentage of extractives.			
Cholesterin	5.4	7.50	51.018	33.282
Lecithin	41.4	73.40	17.442	12.454
Nitrogen	1.8	2.81	2.527	5.558
Free fatty acids	8.0	6.40	14.101	0.000
Combined fatty acids	28.6	11.70	29.344	72.048

Discussion of Chemical Findings. At the present status of our knowledge of the chemistry of organs we do not feel warranted in drawing any very definite conclusions from the analysis of three spleens. It is interesting, however, to point attention to the similarity of the chemical findings in Cases I and II and the variation in Case III. The cholesterin-lecithin fraction of the extractives in all three cases varies from 46 to 80 per cent. There is no great variation in the total amount of cholesterin in the first two cases; in the third case, however, the cholesterin figure is much higher. This again illustrates the well-known fact that microchemical examination is no index of quantitative chemical determinations. Despite the seemingly large amount of cholesterin in Case III the microchemical tests here, as well as in Cases I and II, gave absolutely no indication of its presence.

We are presenting these figures as a matter of record, with the hope that chemical analyses of normal and pathological spleens in the future may throw more light on this obscure condition. A critical study of the findings, however, may warrant the assumption that the peculiar substance in the cells, which is so characteristic of Gaucher's disease and which has never reacted to any microchemical method for lipoids, is not of pure lipoid nature. The substance does not lie in the extractive group, but is, in all probability, of complex protein nature in combination with lipoids.

CONCLUSIONS. Gaucher's disease is characterized by a distinctive, well-defined clinical picture and constant, definite changes in the hemopoietic organs. The presence in these organs of peculiar large cells with a characteristic type of cytoplasm, not duplicated in any other disease, is a distinguishing histological feature. These cells are derived from the reticular apparatus of the hemopoietic structures, but an additional origin from the endothelial cells of the venous sinuses of the spleen cannot be denied. Fat or lipoid bodies cannot be found in the large cells by microchemical or polariscopic tests. The peculiar substance in the large cells does not lie in the extractive group, on chemical analysis, but is apparently of complex protein nature in combination with lipoids. The disease is evidently caused by some disturbance of metabolism, the products being found in a specific group of cells (reticulo-endothelial) of the hemopoietic system.

Other diseases as well as some lesions produced experimentally in animals may be accompanied by the presence of large cells involving the same specific group of cells that are concerned in Gaucher's disease. This group, as has been shown, may react in various ways to many forms of irritation, chemical, bacterial, metabolic or toxic in character, but the changes in each instance are dependent upon variable etiological factors, and a clear distinction between these cellular reactions and the large cells of Gaucher's disease may be made microchemically and histologically.

LITERATURE CITED.

Anitschkow, N.: Die pathologischen Veränderungen innerer Organe bei experimenteller Cholesterinverfettung, Deutsch. med. Wchnschr., 1913, Band xxxix, 741.

Anitschkow, N.: Ueber experimentell erzeugte Ablagerungen von anisotropen Lipoidsubstanzen in der Milz und im Knochenmark, Zeigler's Beiträge, 1914, Band lvii, 201.

Aschoff, L., und K. Kiyono: Zur Frage der grossen Mononukleären, Folia Hematol. Archiv, 1913, Band xv, 383.

Bernstein, E. P.: Gaucher Splenomegaly Diagnosed by Spleen Puncture before Operation, Jour. Am. Med. Assn., 1915, vol. lxiv, 1907.

Brill, N. E., and F. S. Mandlebaum: Large-cell Splenomegaly (Gaucher's Disease): A Clinical and Pathological Study, Am. Jour. Med. Sc., 1913, vol. cxlvi, 863.

Downey, Hal.: Reactions of Blood- and Tissue Cells to Acid Colloidal Dyes under Experimental Conditions, Anat. Rec., 1917, vol. xii, 429.

Erdmann, J. F., and J. J. Moorhead: Splenectomy for Splenomegaly (Gaucher Type), Am. Jour. Med. Sc., 1914, vol. cxlvii, 213.

Evans, F. A.: Gaucher Splenomegaly in a Child, Proc. New York Path. Soc., 1916, vol. xvi, 114.

Evans, H. M.: The Macrophages of Mammals, Am. Jour. Physiol., 1915, vol. xxxvii, 243.

Gaucher, E.: De l'épithélioma primitif de la rate, Thèse de Paris, 1882.

Goldmann, E. E.: Neue Untersuchungen über die äussere und innere Sekretion des Gesunden und kranken Organismus im Lichte der "vitalen Färbung," Tübingen, 1912.

de Jong, R. de J., und J. S. van Heukelom: Beitrag zur Kenntnis der grosszelligen Splenomegalie (Typus Gaucher), Ziegler's Beiträge, 1910, Band xlviii, 598.

Kiyono, K.: Die vitale Karminspeicherung, Jena, 1914.

Knox, J. H. M., Wahl, H. R., and Schmeisser, H. C.: Gaucher's Disease: A Report of Two Cases in Infants, Johns Hopkins Hosp. Bull., 1916, vol. xxvii, 1.

de Lange, Cornelia, und Schippers, J. C.: Over een weinig voorkomend familiair lijden (waarschijlijk splenomegalie type Gaucher), Nederl. Tijdschr. v. Geneesk., 1917, i, 890.

de Lange, Cornelia, und Schippers, J. C.: Familial Splenomegaly: A Clinical Study, Am. Jour. Dis. Children, 1918, vol. xv, 249.

Lutz, W.: Ueber grosszellige Hyperplasie der Milzpulpa bei diabetischer Lipämie, Ziegler's Beiträge, 1914, Band lviii, 273.

Mallory, F. B.: A Histological Study of Typhoid Fever, Jour. Exper. Med., 1898, vol. iii, 611.

Mandlebaum, F. S.: A Contribution to the Pathology of Primary Splenomegaly (Gaucher Type), with the Report of an Autopsy on a Male Child Four and One-half Years of Age, Jour. Exper. Med., 1912, vol. xvi, 797.

Mandlebaum, F. S., and Downey, Hal.: The Histopathology and Biology of Gaucher's Disease (Large-cell Splenomegaly), Folia Hematol., 1916, Band xx, Archiv, 139.

Mandlebaum, F. S., and Downey, Hal.: The Cases of Gaucher's Disease Reported by Drs. Knox, Wahl and Schmeisser, Johns Hopkins Hosp. Bull., 1916, vol. xxvii, 109.

Reuben, M. S.: Gaucher's Disease, New York Med. Jour., 1918, vol. cvii, 118.

Risel, W.: Ueber die grosszellige Splenomegalie (Typus Gaucher), Ziegler's Beiträge, 1909, Band xlvi, 241.

Rössle, R., und Yoshida, T.: Das Gitterfasergerüst der Lymphdrüsen unter normalen und pathologischen Verhältnissen, Ziegler's Beiträge, 1909, Band xlv, 110.

Schlagenhaufer, F.: Ueber meist familiär vorkommende, histologisch charakteristische Splenomegalien (Typus Gaucher), Virchows Archiv, 1907, Band clxxxvii, 125.

Schultze, W. H.: Ueber grosszellige Hyperplasie der Milz bei Lipoidämie (Lipoidzellenhyperplasie), Verh. d. deutsch. pathol. Gesellsch., 1912, Band xv, 47.

Tschaschin, S.: Ueber die "ruhenden Wandersellen" und ihre Beziehungen zu den anderen Zellformen des Bindegewebes und zu den Lymphozyten, Folia Hematol., 1913, Band xvii, Archiv, 317.

Williams, J. R., and Dresbach, M.: A Fatal Case of Diabetes Mellitus Associated with Large-cell Hyperplasia, Am. Jour. Med. Sc., 1917, vol. cliii, 65.

STANDARDIZATION OF METHODS IN CASES OF PROSTATIC OBSTRUCTION.

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THAT marked benefits follow the standardization of methods in medical therapeusis is a fact sufficiently patent today to need no detailed emphasis. While the setting up of established rules is of value in any branch of science, it is especially in those branches dealing with the actual treatment of disease entities that the most direct and gratifying results are obtained. In no instance is this seen more clearly than in the history of surgical procedures of all kinds. Consider, for instance, a single illustration: the surgery of hernia. In his article in Keen's surgery, Coley states that in 1890 the most reliable statistics of the results of operation showed from 30 per cent. to 40 per cent. relapses within the first year; and an immediate operative mortality of about 6 per cent. Today the operation is followed by permanent cure in about 95 per cent. of all cases and the operative mortality has fallen to one-quarter or one-half per cent. These marked improvements have been due in greatest measure to standardization of method (Bassini), and to a clearer and more widely diffused knowledge among surgeons of the principles underlying operative treatment. Similar improvement can be demonstrated to have followed our dealings with the appendix; the cancerous breast or uterus; the stomach, gall-bladder and intestines.

Before becoming well established and of universal application almost all surgical operations have gone through four stages. The first is when the operation is performed by a few pioneers, often men ahead of their generation in ability and imagination; always clear thinking, hard struggling. Later there comes a more universal adoption, as the knowledge of the benefits to be hoped for becomes diffused, till a third stage is reached when the operation though widely attempted is sometimes handicapped by modifications of many sorts; often unnecessary, frequently harmful. With the passage of time, however, the unnecessary is dropped, the essential retained and a few basic rules established; in short, the operation becomes standardized and the real permanent benefit in the immediate mortality and remote results is seen.

The treatment of cases of prostatic obstruction is at present just entering this final stage. Even today one may find the mortality following operation as high as 15 or 20 per cent. in some instances, whereas in the hands of many others this has been reduced to from 6 to 3 per cent. or even less. Efforts to standardize the treatment

and operation are constantly being made, but it is evident that more still are necessary.

The surgical problem of the patient afflicted with prostatism is peculiar in that he is usually at an age of declining vigor. It is very exceptional to find such a patient whose heart and kidneys are still normal. Standardization of the methods of preoperative treatment therefore is of the first and utmost importance. Besides the local condition at the bladder outlet the general condition of the patient in each instance demands careful attention.

The general examination should consider in all cases the normality, or degree of departure from this, of the circulatory system. The blood-pressure, both systolic and diastolic, should be measured and charted. If there is any very evident abnormality of the heart action an analysis of this by the electrocardiograph often gives a clear index for treatment before venturing on operation. The fact that many of these patients are tending toward uremia should never be forgotten, and special watch should be kept for signs of acidosis. Headache, occasional slight mental confusion, dry mouth and tongue and buccal dysphagia are the earliest signs which in my experience point to impending uremia. Occasionally mild grades of the dyspnea of acidosis are seen.

Of even more importance than the condition of the heart is that of the kidneys, so that the renal function should be considered most carefully. An estimation of the ability of the kidneys to excrete foreign dyes is judged by the injection of phenolsulphonephthalein, while the degree of retention of waste products is found by measuring the urea nitrogen of the circulating blood. These two tests form the basis of all successful preoperative care of prostatic patients and should be carried out frequently. Of special importance in the examination of the urine is its quantity, which should be noted each day together with the specific gravity. An output greater at night than during the day, and of a persistently low gravity, is significant of serious renal damage. Note should also be made of the degree of infection of the bladder and kidneys as estimated by the amount of pus which the urine contains. As is well known, the prostatic with uninfected urinary system is often a poorer operative risk than the patient who being infected has established a resistance thereto. That the infected patient is a better risk is only relatively true, however, for it is often with signs of entire failure of renal function from overwhelming pyelonephritis that such cases die. There, is, therefore in every case a clear indication for doing whatever is possible to prevent infection and to help the patient to fight it when it exists.

An adequate knowledge of the local conditions at the neck of the bladder is imperative. By rectal touch one determines the size of the prostate, its consistency, its degree of tenderness, as well as whether or not it is adherent and whether or not the notch is preserved. By catheter the amount of retained urine is noted and by

cystoscope the exact configuration of the obstructing masses as well as the presence or absence of bladder stone, diverticulum or tumor are learned. I am strongly of the opinion that with a very few special exceptions no surgeon is justified in undertaking the operative removal of a prostate which he has not previously examined *personally*, both by rectal touch and by cystoscope. He certainly will not so operate if he desires the lowest possible mortality rate. It is well to remember that cases of obstruction to urination occur frequently in which no enlargement of the prostate by rectal touch can be found. In these instances the difficulty is caused by a median bar or middle-lobe hypertrophy, conditions which can only be determined by the cystoscope. In such cases palpation of the prostate by rectum while the cystoscope still fills the urethra is enlightening.

A clear recognition of the great importance of the factor of urinary retention in causing back pressure on the kidneys, and thus seriously interfering with their functional power, has been the most notable contribution during the last decade to the subject of prostatism. Therefore the surgeon's first and most pressing duty is to relieve the retention and put the bladder at rest. There are two methods by which this can be accomplished: either by the use of the constant inlying catheter or by an artificial opening made in the bladder above the pubes. Each method is equally efficient, and according as the other factors enter, such as the type of prostatic enlargement and the kind of operative attack proposed, will the choice of one or the other be made.

With the above considerations in mind the preoperative care of the prostatic will be seen to be well standardized by the following rules used at present in the Peter Bent Brigham Hospital.

Preoperative Treatment and Management of Cases of Prostatic Obstruction. *Forcing Fluid.* Each case of prostatic obstruction is to be given water by mouth as follows: every hour during the day 180 to 200 c.c. The same amount every three hours at night. If the patient cannot take approximately this amount of water the difference should be made up by rectal injection or hypodermoclysis. Cardiac complications are a contra-indication to this procedure. Record the fluid intake and output on the chart.

Urinary Antiseptics. In all cases give hexamethylenamin, grams 1.0 t. i. d., after demonstrating the fact that urine is acid. If this is not the case give sodium benzoate, 0.5 gram t. i. d., until acidity is established, then give hexamethylenamin.

Urine Analysis. Every other day, or oftener if the condition necessitates, an analysis of the urine is to be made from the twenty-four-hour specimen and recorded. This includes the microscopic examination of sediment as well as the estimation of its amount.

Diet and Bowels. The diet should be liberal. House diet is sufficient as a rule. Special attention should be paid to keeping the bowels active, so that at least one dejection is obtained each day.

Blood-pressure. Blood-pressure readings should be made on the entrance of the patient and at least every three or four days thereafter.

Relief of Urinary Obstruction. All cases showing residual urine on entrance should have the bladder put at rest by one of three means: (1) inlying catheter; (2) intermittent catheterization; (3) suprapubic cystotomy.

Every catheterization should be done under rigid aseptic precautions. The operator's hands should be washed with soap and water, alcohol or corrosive. The penis should be washed with soap and water and corrosive. Sterile forceps are better than the hand for inserting all catheters except those bearing a stylet. The safest lubricant is glycerin, recently sterilized.

Inlying Catheter Routine. If possible this should be a soft-rubber instrument, size 24 to 26 F., passed on a wire stylet. It should be attached in place by adhesive strapping. Wash the bladder through the catheter each morning and night, using 1 liter of warm 1 to 60,000 bichloride of mercury or 1 to 5000 silver nitrate. Do not distend the bladder over 200 c.c. at a time. Failure of the catheter to drain at any time should be immediately reported by the nurse to the surgeon in charge of the ward. Remove the catheter every three days and wash out the urethra from the meatus with 1 to 5000 silver nitrate. Reinsert the catheter (reboiled or a new one) in from four to six hours.

Except when there is some contraindication, such as cardiac decompensation, the patient should be urged to be up and about the ward in a chair or walking a little each day. Under these conditions the catheter can be corked. It must be opened every four hours to empty the bladder.

Watch for any evidence of infection, such as severe urethritis (tenderness of urethra as palpated over catheter) or epididymitis, and in such cases remove the catheter and wash out the bladder and urethra with 1 to 5000 silver nitrate. Then employ:

Interval catheterization, passing the instrument every six hours during the day and once during the night. Inject into the bladder 50 c.c. of 1 to 10,000 silver nitrate after each operation and allow it to remain there.

Suprapubic cystotomy should be reserved for those cases in which, because of infection, severe pain or bleeding, catheterization cannot be instituted.

The Phenolsulphonephthalein Test. This should be carried out on each case on admission and every fourth day thereafter until operation.

Empty the bladder by the catheter. Inject intramuscularly 6 mg. (1 c.c.) of dye and note the time of the injection. Collect the urine coming from the catheter immediately after the injection into a flask with 2 to 3 c.c. of 10 per cent. sodium hydroxide and note the

appearance time of the dye. One hour later collect the urine and again at the end of the second hour. Estimate the percentage of dye in each collection separately. This should be done by daylight or white artificial light, and within a short time after the last collection is made.

Blood Urea Nitrogen. Ten cubic centimeters of blood are to be collected from an arm vein under aseptic conditions and sent to the laboratory technician for estimation and report.

The three groups of phenomena in these cases to be watched for and guarded against are those of (1) increase of infection of any part of the urinary passages, (2) uremia, (3) cardiac decompensation.

Careful observation of the patient's condition under such a régime as this will determine the time when the operation may safely be undertaken. It is important not to be deceived by a phthalein reading well within the normal limits (even 40 to 50 per cent.) when the patient is first seen, especially if he has a large amount of residual urine. Such readings are often seen to fall sharply during the first days of bladder drainage. But as the relief of back pressure on the kidneys continues, their function becomes slowly better, so that when the output of the dye has reached a stable figure, an operation may safely be attempted which would have been most hazardous earlier.

The time devoted to preparation of the patient for operation is thus seen to be a very variable one. In our experience it has averaged about a week or ten days; but this may be reduced to three or four days in some cases, while in others a month or more of preoperative care is necessary.

Two ways of reaching the prostate exist—through the perineum and transvesically—and while it is not our purpose to describe these operations in detail here, it will be necessary to give a brief outline of each, especially as regards its applicability under differing conditions:

The Perineal Operation. The earliest operations for removal of the prostate followed the perineal approach, and although many difficulties were experienced by the pioneer operators, this approach as modified by several surgeons, especially Young, is still of great value and should be the method of choice in many instances.

The two outstanding advantages of the perineal operation as compared with the suprapubic lie in the control of hemorrhage and in the easy and short convalescence. The gland having been removed there is left a cavity *external* to the bladder itself which can be nicely and accurately packed with gauze in a manner quite impossible when the approach has been transvesical. Also, for reasons not always quite clear, this form of operation is well known from clinical experience to cause less immediate prostration to the patient. Each of these points plays a part in promoting a quick, relatively comfortable convalescence.

A still further and very important advantage of the perineal operation is in regard to the question of malignancy. The incidence of prostatic cancer is unfortunately quite high, some clinics finding it in as much as 20 per cent. of their cases. This is probably a greater proportion than that seen, as a rule. In our own experience about one of each eight or ten cases is found to be malignant. The malignancy *always* begins in the posterior lobe, that portion of the gland which is first seen and examined by the perineal operation, but not seen at all by the transvesical approach. In any case, therefore, where the least suspicion of malignancy has been raised by the clinical examination, operative investigation of the gland from its perineal aspect is imperative.

The most marked disadvantage of the perineal approach lies in the fact that it is a relatively difficult operation in the hands of those who have not given special attention to perfecting themselves in it in all its details. The anatomical proximity of the prostate to the rectum has sometimes led to wounds of this structure and susequent fistula. In other instances opening the urethra at a point too far below the tip of the prostate, and thus cutting the external or voluntary sphincter, has led to incontinence, partial or complete. Furthermore, unless the operator has been able to make a careful cystoscopic survey of the prostate before operation, he may by the perineal route overlook an hypertrophied middle lobe and find his patient after the operation still unable to empty the bladder with success in spite of the fact that "the prostate has been removed." I have personally seen instances of each of these difficulties.

For these reasons, especially, the perineal operation has failed to gain in popularity in the eyes of many surgeons. That this lack of popularity is undeserved I am sure anyone will quickly admit should he have the opportunity to follow to the end-result a series of cases of prostatectomy performed by this route and to compare this with a like series done by the suprapubic method. The situation may fairly be summed up by the statement that the perineal operation is harder on the surgeon than the suprapubic, but is easier on the patient.

To overcome the difficulties of the perineal operation three things are necessary: (1) the surgeon himself must be able to use the cystoscope and to *understand what he sees;* (2) he must know the anatomy of the perineum accurately, both in the cadaver and in the living patient; (3) he must have the operating room facilities for placing his patient in the high lithotomy position, which can only be secured by the use of a board such as that devised by Professor Halsted, since no operating table yet on the market will give sufficient elevation. The exaggerated position is absolutely essential, since it puts the perineal structures on the stretch and makes it possible to do the whole operation under the guidance of the eye. Only too often have I seen a surgeon vaguely operating in the depths of a

perineal wound, unable to see, uncomfortable and uncertain of just what structures, or portions thereof, were being removed; and all the difficulty due to the fact that he had his patient in the low lithotomy position, such as is used for a curettage of the uterus or the removal of hemorrhoids.

A brief summary of the steps of the removal of the prostate by the perineal route is as follows: The patient should be placed in an exaggerated lithotomy position; the incision should be made with anterior curve connecting each ischial tuberosity with the bulb of the urethra; exposure of the membranous urethra and introduction of tractor through a longitudinal incision in same; exposure of posterior surface of the gland and palpation for areas of possible malignancy. Vertical incisions into prostate on either side of the midline, through which lateral lobes are enucleated. Removal of tractor and insertion of index finger to palpate the region of the median lobe. If this be found enlarged, it should be enucleated. Insertion of a No. 30 F. soft-rubber catheter into the bladder and packing of each lateral cavity about this tube with gauze tape impregnated with kephalin. Union of the levator ani muscles in front of the rectum with one catgut stitch and closure of the wound. On being placed in bed the patient is immediately given 750 c.c. of saline solution by hypodermoclysis.

The Suprapubic Operation. The transvesical approach to the prostate has many warm advocates, and when used in properly chosen cases, removal of the gland by this route is an eminently satisfactory operation. Since it can easily be performed in two stages, it permits easy and safe drainage of the bladder and consequent relief to the kidneys by a simple cystotomy above the pubes under local anesthesia. Later, the condition of the patient having improved, the prostate can be enucleated in a short operation performed under free view and with accurate appreciation of the obstructing mass by bimanual palpation.

In any considerable number of patients suffering from prostatism in whom it is imperative that the bladder be put at rest and the kidneys relieved, there will be found not infrequently cases that cannot tolerate an inlying urethral catheter. The reason for this is usually found in an acute infection of the prostate and prostatic urethra coexisting with the enlargement. In the hands of a skilful, especially trained orderly or nurse such cases can be tided over the acute discomfort to a stage in which the catheter is satisfactorily tolerated. But such assistants, experienced in all the numerous minor adjustments necessary in difficult cases, are not always at the command of even the best-equipped hospitals. The efforts of the average house surgeon are rarely of avail. Repeated ill-advised manipulations with frequent prodding by catheters of varying sorts only increase the discomfort of the patient, which is already great, and make for increase of infection

and irritability of the already swollen prostate. Under such circumstances the bladder should be opened above the pubes forthwith.

The suprapubic operation will also strongly appeal to those surgeons who are unfamiliar with the use of the cystoscope as a means of preoperative diagnosis. With the bladder open they can see definitely that with which they must deal. Another group of surgeons, entirely unfamiliar with the proper type of perineal operation, will naturally choose the easier operation.

But leaving such instances aside, and omitting from consideration prostatic malignancy, let us ask the nature of the disadvantages of the suprapubic operation. To my mind there are two: a major one and a minor one.

The first of these concerns the control of hemorrhage after enucleation has been performed. One has but to review the several devices and methods still employed to appreciate quickly that there is no one of them in general favor. One surgeon uses pressure by the Hagner bag or a modification of this; another packs the cavity with gauze for a longer or shorter time; still others employ sutures or ligatures. The truth is that the mechanical situation which leaves a cavity containing torn vessels, often of considerable size, uncontrolled at the most dependent portion of the bladder, which must inevitably contain urine and often bacteria, and which must be drained against gravity, is inconsistent with the laws of sound surgical practice. The danger of postoperative hemorrhage is therefore an ever-present one, for the prevention of which measures should always be carefully taken.

The second disadvantage of the suprapubic operation concerns, as a rule, only those cases which have had the so-called two-stage operation, and is that of imperfect and slow healing of the twice-opened wound through the abdominal wall and bladder. After the abdominal muscles and bladder wall have tolerated the presence of a constant drain for ten days or more there is often found a lack of plasticity resulting from the infiltration of the tissues by an inflammatory reaction sometimes of considerable extent. This not only makes a second entrance into the bladder at this time more difficult than at the first operation, occasionally carrying the risk of inadvertently opening the peritoneal cavity, but it also prevents speedy and firm closure of the structures involved. Thus the convalescence after a two-stage suprapubic prostatectomy is frequently tedious and annoying for the patient. The constant presence of dressings saturated with urine, unless some special means be employed to avoid this, is also often extremely distasteful to patients of a certain type.

It is clear that if the methods of preventing postoperative hemorrhage can be standardized, this most prominent objection to suprapubic prostatectomy will be controlled. Although, as mentioned already, the measures advocated for this purpose are numerous, I

am sure that only when such measures include the basic surgical principles of exact ligature or suture of definite bleeding-points will they prove continuously of avail, and therefore become standard. I wish strongly to advocate, therefore, a suprapubic opening of the bladder throughout almost the entire extent of its anterior aspect, thus making possible adequate retraction and easy access to the region of the neck of the bladder after the prostate has been removed. Following this removal the cavity is best temporarily packed with gauze or tape impregnated with some styptic, such as kephalin. This is left in position for a few moments, and after its removal all those bleeding points which remain are controlled by accurate ligatures of plain catgut passed on a curved needle. Naturally such a procedure adds a few minutes to the duration of the operation, but there is no doubt that the safety of the patient and peace of mind of the surgeon thus secured, are well worth the extra time.

It is thus seen that the practices of the "five-minute prostatectomist" are to be entirely condemned. No doubt anyone foolish enough to attempt it can hastily insert one or two fingers into the bladder through the opening made at an earlier operation, tear out the prostate, adjust a large tube in the abdominal wall and get the patient off the operating table all in five minutes. It is possible to do this, but no patient is a fit subject for such a major operation as that of prostatectomy if his condition is so poor that it will permit of but five minutes of general anesthesia. The grave dangers of such haphazard operating are self-evident, and have done much in the past to keep high the mortality of this special operation. Fortunately operators so little cognizant of the principles of good surgery are not common today.

In regard to the second and less important difficulty which concerns slow healing of the suprapubic wound, we must accept this as in a measure inevitable. Careful mobilization of the anterior wall of the bladder from the under surface of the recti, mobilization also of these muscle bellies behind their sheath, followed by accurate approximation and suture, will do much toward promoting an early closure. If facilities are at hand for the proper care of such suction apparatus as that of Bethune, its use will go far toward the comfort of the patient by keeping the dressings almost, if not quite dry. An outline of a standard two-stage prostatectomy is as follows:

First Operation. *Suprapubic Cystotomy.* Local anesthesia with one-half of 1 per cent. novocain. Patient in slight Trendelenburg position. Infiltration of the skin in the middle line above the pubes for a distance of about 7 cm. Incision of the skin and subcutaneous tissue down to anterior rectus sheath. Infiltration into and below this sheath. Incision of sheath and retraction of muscle bellies. Infiltration of bladder wall and pushing upward of peritoneal reflection. Small incision of bladder wall between guides down to mucosa, which pouts into the wound. Use of aspirating

trocar or catheter to empty the bladder. Incision of mucosa and quick, gentle exploration of the bladder by the finger. Adjustment of a self-retaining catheter in the bladder. Suture of the wound with a small drain of rubber tissue in the anterior vesical space.

SECOND OPERATION. *Transvesical Prostatectomy.* General anesthesia by gas and oxygen. Patient in moderate Trendelenburg position, with legs covered by separate blankets, leaving region of anus accessible. Careful reopening of wound in skin and muscles down to the bladder. The finger in the cystotomy opening directs incision of the anterior bladder wall downward to within 2.5 cm. of the prostate. Introduction of self-retaining retractor and wide exposure of bladder neck. Insertion of two fingers of the left hand into the rectum, and with this support the prostate is enucleated from above. With continued support by the rectum, the cavity is packed with kephalin gauze under pressure. Removal of the gauze and control of the bleeding-points by suture. Double layer of interrupted sutures in the anterior bladder wall. Large drainage tube adjusted in the upper angle of the wound. Accurate approximation of structures of the abdominal wall by suture. Hypodermoclysis of 750 c.c. of saline solution.

The factors which lead to the choice of either the perineal or suprapubic form of prostatectomy are therefore seen to be five in number. In the first instance the choice is determined by the condition of the patient and of his bladder and urethra. If it be possible to explore the bladder satisfactorily by the cystoscope and adequate constant drainage by inlying catheter can be instituted for a sufficient period of time the perineal operation will be chosen. It will also be our choice in any case presenting areas of questionable malignancy on rectal palpation. All cases in which the urethral catheter cannot be borne, or those in which the element of infection in prostate, bladder or possibly kidneys is predominant, will demand the suprapubic operation in two stages. It is also wisest to approach all cases showing diverticula or tumor of any considerable size by the suprapubic method, since in many such instances removal of the prostate must be accompanied by excision of the diverticulum or tumor ere the patient be entirely free from difficulty. Stones of any usual size can be removed equally well by either route. And, finally, choice of operation will be determined by the experience of the individual operator in one form or the other of operation, together with his ability or inability to use a cystoscope.

It is my hope and expectation that through the growing recognition by the general surgeon of the principles to be followed in the removal of a prostate the time is not far distant when the operation will have become standardized and the patient thus be offered increased safeguards.

THE NERVOUS SYMPTOMS IN PERNICIOUS ANEMIA: AN ANALYSIS OF ONE HUNDRED AND FIFTY CASES.[1]

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It was not without some hesitancy that I selected this particular topic, since the literature on the subject is already voluminous, and additional contributions would almost seem unwarranted. A careful review of the subject, however, reveals that many of our pet views concerning pernicious anemia rest on a foundation that is indeed insecure; that there is existing the widest divergence of opinions, some of which may possibly be brought into harmony by facts that may be gleaned from the analysis of a larger number of cases; and that fundamental problems are still left entirely unexplained, the inherent perplexities of which greatly augment our desire to aid in their solution.

"The mind occasionally wanders," said Addison, when, in 1855, he gave to the world his classical description of idiopathic, pernicious anemia. This statement practically summed up what was known of the central nervous system in its relation to pernicious anemia until 1886, when Lichtheim described three cases of the condition, which presented symptoms ordinarily seen in tabes. Although Lichtenstern, two years prior to this, had published an article entitled "Progressive Pernicious Anemia in Tabetics," in which he considered the pernicious anemia to be dependent on the tabes, it was Lichtheim who first recognized the true significance of this syndrome.

The resemblance of these cases, both clinical and particularly anatomic, to tabes dorsalis, is however, only superficial. The changes in the cord have been longest known and studied in great detail. Here the degeneration is seen to begin as small, isolated plaques, with primary involvement, as a rule, of the posterior columns, later of the lateral columns also. These plaques, by confluence and secondary degeneration, ultimately bring about a diffuse and extensive disintegration of the white matter of the cord, known as subacute combined sclerosis. Although the brain was for a long time thought not to be involved in this type of degeneration, investigations of the past four years have revealed definite areas of destruction here also. Nor is pernicious anemia alone responsible for this particular type of subacute degeneration. Among the causes are the leukemias, Addison's disease, probably very severe secondary anemias, diabetes, nephritis, senility and arteriosclerosis, pellagra, tuberculosis, syphilis, leprosy, malaria, typhoid, septicemia,

[1] Presented before the Minnesota State Medical Association, August 29–30, 1918, Duluth, Minn.

scarlet fever, diphtheria, influenza, chronic alcoholism, lead, phosphorus, arsenic—in short, degeneration in the nervous system may be the concomitant of almost any chronic intoxication. And, too, in pernicious anemia it is not the anemia so much as the associated toxin or toxins, that is responsible for the damage done the central nervous system.

The obvious conclusion, after a perusal of so long a list of etiologic possibilities, would be that pernicious anemia forms an etiologic basis in but a small fraction of the cases of combined sclerosis. This is by no means true. Dana estimates this at about 10 per cent.; Taylor at 12 per cent.; von Voss, basing his estimate on published cases of combined sclerosis, found pernicious anemia to be responsible in about one-third of the cases, which is approximately the percentage noted at the Mayo Clinic.

To what extent secondary anemia may be responsible for the production of a combined sclerosis of the cord is by no means established. According to Clark, more of the anemias seen in this relationship are secondary than primary, though, he adds, these changes are usually not looked for in secondary anemias. Bramwell, taking the opposite stand, states that in many of these cases, in which the anemia does not conform to the pernicious anemia type, subsequent development will show it to be so. While we can offer no definite figures in this connection, our experience confirms the latter position. The difficulty of deciding this point is greatly increased when one recalls that in secondary anemia the cause of the anemia may easily be the cause of the combined sclerosis, and that severe anemias in young persons, in whom the anemia is not dependent on some toxic factor, are comparatively rare.

The estimation of cord changes present in pernicious anemia patients is variable and ranges from the general statement that it is present, "not in many cases of pernicious anemia" (White), to percentage estimates of approximately 2.8 (Bramwell); 11.7 (Nonne); 25 (McCrae); 40.9 (McPhedran) and 50 per cent. (Henneberg). Since some of these figures were published, the technic of neurologic examinations has been greatly refined so that more accurate observations are possible. Doubtless the percentage of cases of pernicious anemia presenting evidence of cord involvement is considerably higher than any of the foregoing figures. Of 282 unquestioned and not otherwise complicated cases of pernicious anemia seen at the clinic since 1916, 150 were subjected to a detailed neurologic examination, of which no less than 80.6 per cent. presented indisputable evidence of the destruction of nervous parenchyma.

Approximately 12.7 per cent. of the patients came for the express purpose of seeking relief from symptoms directly attributable to involvement of the nervous system. Chief among these were the paresthesias, especially numbness and tingling of the hands and feet, which were present in about 80 per cent. of all cases, regardless

of whether or not involvement of the nervous system could be demonstrated objectively. This was expressed variously; patients complained that their hands and legs felt dead; that their "legs felt like sticks," or "like wood to the hips," "as though in a cast," or that "the hands and feet felt padded," "like thawing out after being very cold," and "as though the limbs were filled with innumerable ticking watches." In some instances the entire body was numb, again some particular part, as the tongue alone. One patient complained that the buttocks were numb and felt much bigger than normal. Many complained of feeling cold all the time, especially in the feet or in the knees, "as though a draft were blowing on them." In one case the teeth and gums felt so cold as to cause the patient great discomfort. A goodly number complained of burning. Some had sticking, stinging pains in the limbs, as if they had been stung by some insect. One woman repeatedly had her daughter look for glass slivers which she thought must be embedded in her finger-tips. Shooting pains or tingling over a large surface occurs at times when some part of the body is touched, as with cottom or with a pin. Occasionally a patient complains of a girdle pain (2.8 per cent.), or the sensation of a tight band drawn around the knees (1.7 per cent.). A number presented themselves for examination because of inability to control the arms and legs properly. One of these, a conductor, was seriously handicapped in his work because of the difficulty he experienced in selecting the proper coins by the sense of touch.

In the motor field, cramping of the calves occasionally proved to be the source of great discomfort. One patient complained principally of tremor. Another exhibited such marked, choreiform movements that she would repeatedly drop objects and fed herself only with great difficulty. In one instance a hemiplegic attack of three days' duration was seen.

In relation to the cranial nerves, diminution in the senses of smell, taste and hearing was noted. A central scotoma gave one patient great inconvenience. Disturbances of taste are not infrequent; to one patient everything tasted sour; to another, bitter, and a third, with normal mentality, included in her dietary egg shells and soft rocks, which she carefully selected. Symptoms referable to disturbance of the eighth nerve, especially roaring, ringing or thumping in the ears, are very common. Sometimes there is a distressing dizziness, and now and then fainting spells are noted.

As to the relationship between the time of onset of the disease, dating this from the first characteristic symptom and the time of onset of the nervous symptoms, there is nothing constant whatsoever. Thus, a patient may die of pernicious anemia without ever presenting any evidence of central nervous system involvement; on the other hand, the appearance of nervous symptoms may antedate the onset of the anemia, as pointed out by Nonne and Bastianelli. This was true in 1.4 per cent. of our cases, the symptoms

that preceded being usually the parasthesias. In one case, the patient had to resort to the use of crutches and catheterization before any anemia was apparent. The longest time interval noted was thirteen months. The duration of the anemia also showed no definite relationship to the time of onset in the nervous symptoms, though in the cases examined the mean duration of the anemia was 2.2 years and the mean onset of the nervous symptoms ten and one-half months later.

TABLE I.—NEUROLOGICAL DIAGNOSIS BASED ON THE EXAMINATION OF ONE HUNDRED AND FIFTY CASES OF PERNICIOUS ANEMIA, IN 80.6 PER CENT. OF WHICH THE CENTRAL NERVOUS SYSTEM SHOWED INVOLVEMENT.

	Per cent.
Subacute combined sclerosis type of lesion	99.2
Posterior sclerosis	52.2
Combined sclerosis	45.4
Lateral sclerosis	0.8
Multiple peripheral neuritis also present	4.9
Transverse myelitis with primary optic atrophy	0.8

A glance at Table I makes it at once apparent that the type of lesion *par excellence* of the nervous system, as evidenced clinically, is a subacute combined degeneration of the cord, regardless of whether this begins in the posterior or the lateral columns or in both simultaneously, though the columns of Gall and Burdock are in the majority of cases first and most extensively involved.

Primary optic atrophy was seen but once, and, as Collier has emphasized, does not form a part of the picture. Why it should be present in this particular case is difficult to say. Doctor Collier has called attention to the possibility of lues being a factor in these cases. This assumption may be supported here by the finding of a transverse myelitis also, which is certainly uncommon in pernicious anemia, though by no means impossible, yet all other evidence pointing to this complication was lacking.

Of considerable interest is the finding of multiple neuritis, which could be demonstrated in addition to the spinal cord lesion in 4.9 per cent. of the cases. Why a multiple neuritis is not found more frequently at necropsy is a fact rather difficult to bring into harmony with clinical experience, for, as this series shows, a neuritis is not so uncommon. In the vast majority of autopsied cases reported, however, the peripheral nerves were either not studied or no mention was made of them. I have been able to find but 2 cases in the literature in which degeneration was demonstrated in the peripheral nerves at necropsy. Von Noorden reports a case with parenchymatous degeneration in the N. tibialis and N. peroneus and Eisenlohr in the N. Saphenous dexter. Doubtless, careful studies of necropsy material in selected cases would reveal neuritic processes to be more common than seems now to be the case.

While it is obviously impossible to submit detailed reports of all of these cases, Table II represents, in brief, the nervous findings noted in their examination. The various headings have been arranged in order of their importance from a diagnostic standpoint rather than in a sequence which would otherwise be more logical.

TABLE II.—RÉSUMÉ OF FINDINGS IN ONE HUNDRED AND TWENTY-ONE CASES OF PERNICIOUS ANEMIA WITH COINCIDENT INVOLVEMENT OF THE NERVOUS SYSTEM.

Sensibility.	Diminished.	Absent.
Superficial (tactile, pain, thermal)	42.4	
Deep:		
Joint (toes)	60.0	20.0
Tendon	12.8	0.8
Vibration (256 V)	82.4	33.6
Vibration or joint impaired	92.0	

Fundus.	
Pathologic	63.4
Low-grade retinitis	33.0
Hemorrhagic retinitis	29.6
Primary optic atrophy	0.8

Mentality.	
Apathy and somnolence	28.0
Irritability	9.6
Memory defects	7.2
Dementia	2.4
Emotional instability	3.2
Depression	3.2
Psychosis	0.8
Total	35.2

Reflexes.	Increased.	Diminished.	Absent.	Unequal.
Patellar	39.2	28.8	7.2	14.4
Either patellar or tendo-Achillis	..	..	24.8	21.6
Tendo-Achillis	23.2	46.4	20.8	11.2
Ankle clonus (sustained)	4.8			
Babinski positive	26.4			
Oppenheim	7.0			
Chaddock	2.4			
Rossolimo	1.6			
Mendel-Bechterew	0.8			

Coördination.	Impaired.
Arms	15.2
Legs	55.2
Rombergism	52.0

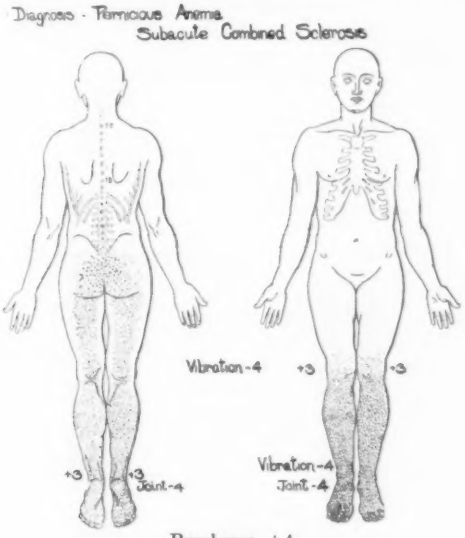
Gait.	
Ataxia	28.8
Spasticity	4.8
Spastic-ataxic	8.0

Urinary Control.	Partial.	Complete.
Incontinence	8.0	0.8
Retention	4.0	0.8

Muscles.	Increased.	Diminished.
Tonus (legs)	16.0	10.4
Power, disproportionately impaired, in legs	..	8.0
Complete paraplegia	..	1.6
Atrophy, localized with fibrillation	..	0.8
Choreiform movements	..	0.8

The cardinal findings anent the objective evidence pointing to involvement of the nervous system occur in the realm of sensation. Superficial sensibility was found to be definitely impaired in 42.4 per cent. of the cases, excluding those in which the diminution was so slight as to be uncertain (Fig. 1[2]).

As Figs. 1 and 2 illustrate, it varied considerably in degree and was usually most marked over the legs and the buttocks, there being no evidence of dissociation of touch, pain or temperature, such as is seen, for example, in tabes (Fig. 2).



Romberg: +4
Tonus: Legs: +3
Coördination: arms −1; legs −4
Gait: marked spastic; ataxic

FIG. 1

More significant still is the disturbance of deep sensibility, particularly of vibration and of joint sensibility, which either single or combined were definitely impaired in 92 per cent. Here, too, the disturbance is, as a rule, limited to the legs, pelvis and lower portion of the spine, the upper portion of the body usually escaping intact. It is a rather striking feature that vibration is more frequently and more markedly disturbed than joint sensibility, albeit both forms of sensation are supposed to travel up the cord in fibers which occupy

[2] The numerals used in the figures represent degrees of diminution or increase on a scale of four, 0 being normal, −4 signifying complete absence, +4 very marked increase. Numerals placed next to the figure and not otherwise explained refer to the condition of the reflexes. The stippling indicates diminution in superficial sensibility. Other findings not charted are normal.

relatively the same position in the posterior column. This was very marked in some cases complete absence of vibration sensibility, or pallanesthesia, over the pelvis and legs being noted in 4.8 per cent., where joint sense in the toes was normal. The reverse was never observed to this extent, although in a number of instances joint sensibility was moderately impaired where pallesthesia was normal. The disturbance in deep sensibility is thus seen to be the most outstanding feature in the entire neurologic examination. In only 2.4 per cent. of cases was the disturbance in superficial sensibility more marked than the diminution in deep sensibility.

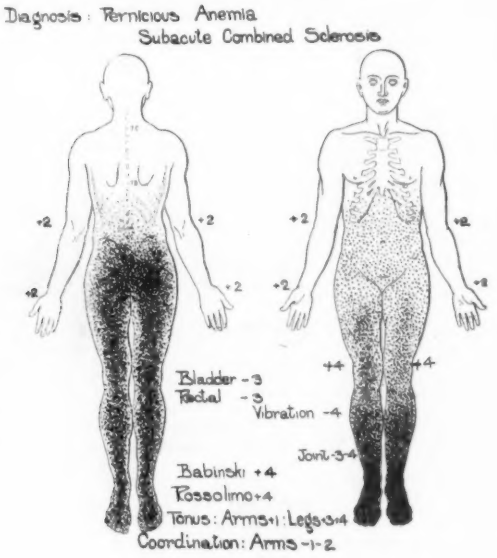


FIG. 2

Within the past few years the psychic phenomena noted in these patients have been exhaustively studied and numerous contributions have appeared, many of them interesting and scholarly, although the texts on psychiatry, on the whole, dismiss the subject with a few remarks or neglect it entirely. A more careful search into the mental condition of these patients would reveal a higher percentage of abnormality than is indicated in Table II, in which only the outstanding features are noted. In only one case was there an outright psychosis present, and this was of the infection-exhaustion type. Here the anemia was ushered in with an acute hallucinatory confusion, which cleared up after three weeks and reappeared once subsequently, *pari passu*, with an aggravation of the patient's physical condition. A number of writers, among them Langdon,

recognize in the psychosis something more or less characteristic, so that a diagnosis of prepernicious anemia has been made in the absence of anemia, which subsequent development of the case confirmed. The majority, however, consider these cases as belonging to the exhaustion type of psychosis, lacking any features which are especially characteristic. Psychoses of the better defined types, such as manic-depressive insanity, are looked on as merely coincident, and have, *per se*, little or nothing to do with the existence of the pernicious anemia.

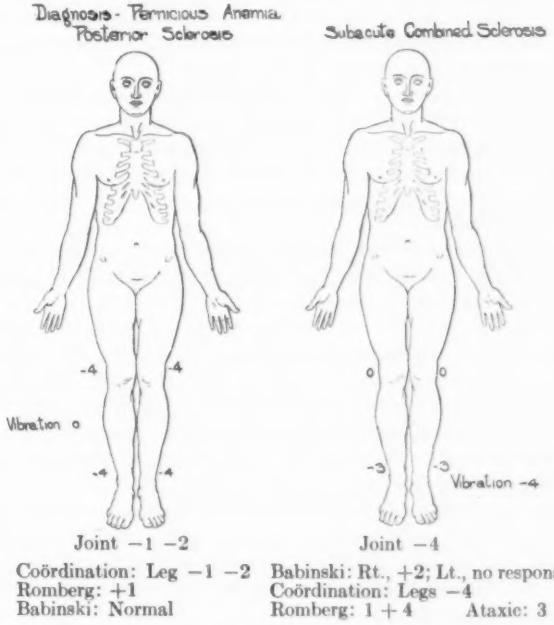


FIG. 3.—On the left, the findings when first seen, on the right, one year and ten months later. Although the knee jerks have returned to normal, due to secondary involvement of the pyramidal tracts, other findings indicate that the degeneration of the spinal cord has progressed and that in spite of a much more satisfactory blood picture.

Relative to the condition of the reflexes, little need be added save in explanation of the chart. The absence of either patellar or tendo-Achillis reflexes, on one or both sides, was noted in 24.8 per cent. and their inequality in 21.6 per cent.

In but one case was there noted a progressive paralysis, with atrophy and fibrillary tremors of the anterior tibial group of muscles on one side, which must be interpreted as a degeneration going on in the anterior horn cells. Doubtless this occurs, though not with the

frequency maintained by Rothmann and Teichmueller, nor yet with the rarity claimed by some of their opponents.

The development of marked choreiform movements in this connection has not, so far as I have been able to learn, been reported before, and is of considerable significance in connection with the pathologic alterations noted in the cerebrum.

Some fourteen years ago a writer on this subject declared that "the study of the spinal cord in pernicious anemia had become an old story." This may be true. The fact remains, however, that our patients still die, and while it may be a long time before any material advance is made in the knowledge of pernicious anemia, our satisfaction with the present status must not act as a shibboleth preventing a better understanding of this disease.

Although the present paper adds little to the knowledge of the condition, I merely wish to emphasize the importance of a correct and early diagnosis in these cases, the prominence which nervous symptoms assume in this disease and the aid which the examination of the nervous system, considering it as a diagnostic measure, may be to the internist.

SUMMARY. The salient points of the knowledge gained by clinical evidence of the relation which the nervous system bears to pernicious anemia may be briefly summarized:

In 80.6 per cent. of moderately advanced cases of pernicious anemia there is indisputable evidence of nervous-tissue disintegration. This is in satisfactory accord with the pathologic findings, of which we may take the figures of Minnich, who demonstrated lesions in the spinal cords of approximately 77 per cent. of cases of pernicious anemia. Subjectively, some form of paresthesia, such as numbness and tingling, is rarely missing.

Objectively, one finds the most striking disturbance in the pathologically altered reflexes, not forgetting the tendo-Achillis and Babinski reflexes and the disturbance of vibration and joint sensibilities, the former of which may readily be tested with almost any type of tuning-fork.

As an adjunct in differentiating pernicious anemia from other anemias the examination of the nervous system will be found of inestimable value; it often forms an easy way out of a most perplexing situation.

REFERENCES.

1. Allbutt, T. C., and Rolleston, H. D.: A system of medicine by many writers. London, Macmillan, 1909, v, 749.

2. Barrett, A. M.: Mental disorders and cerebral lesions associated with pernicious anemia. Am. Jour. Insan., 1913, lxix, 1063.

3. Barrett, A. M.: Mental disorders associated with pernicious anemia. Fifth biannual report, State Psychopathic Hosp., Univ. of Mich., biennial period ending June 30, 1916.

4. Bastianelli, G.: Le sclerosi combinati del midollo spinale nelle anemie perniciosi. Bull. de roy. Acad. de med. di Roma, 1896–1897, xxii, 197; Ref. in Neurol. Centralbl., 1897, xvi, 78.

5. Bramwell, B.: On the association of pernicious anemia with subacute combined degeneration of the spinal cord. Edinburgh Med. Jour., 1915, xiv, 260.
6. Clark, J. M.: On the spinal cord degeneration in anemia. Brain, 1904, xxviii, 441–459.
7. Dana, C. L.: Subacute combined sclerosis of the spinal cord and its relation to anemia and toxemia. Jour. Nerv. and Ment. Dis., 1899, xxvi, 1.
8. Dana, C. L.: Subacute ataxic paraplegia and combined sclerosis—a form of spinal disease associated with lethal anemia and toxemia. Med. Rec., 1899, iv, 897.
9. Eisenlohr: Quoted by Nonne.
10. Henneberg, in Lewandowski: Handbuch der Neurologie. Berlin, Springer, 1911, Spezielle Neurologie, I, ii, 769–793.
11. Langdon, F. W.: Nervous and mental manifestations of prepernicious anemia. Jour. Am. Med. Assn., 1905, xlv, 1635.
12. Lichtheim: Zur Kenntniss der perniciösen Anämie. Verhandl. d. cong. f. inn. Med., 1887, vi, 84.
13. Lichtenstern, O.: Progressive perniciöse Anämie bei Tabeskranken. Deutsch. med. Wchnschr., 1884, x, 849.
14. McCrae, T.: Pernicious anemia. The statistics of a series of forty cases. Jour. Am. Med. Assn., 1902, xxviii, 148.
15. McPhedran, A.: Observations on the nature and treatment of pernicious anemia. Lancet, 1902, i, 148.
16. Minnich, W.: Zur Kenntniss der im Verlauf der perniciösen Anämie beobachteten spinal Erkrankungen. Ztschr. f. klin. Med., 1893, xxi, 25; 264; also 1893, xxii, 60.
17. Nonne, M.: Beiträge zur Kenntniss der im Verlaufe der perniciösen Anämie beobachteten Spinalerkrankungen. Arch. f. Psychiat., 1893, xxv, 421.
18. Nonne, M.: Weitere Beiträge zur Kenntniss der im Verlaufe letaler Anämien beobachteten Spinalerkrankungen. Deutsch. Ztschr. f. Nervenh., 1894–1895, vi, 313.
19. Nonne, M.: Rückenmarksveränderungen in Fällen von perniciöser Anämie, von Sepsis und von Senium nebst Bemerkungen. Deutsch. Ztschr. f. Nervenh., 1899, xiv.
20. Von Noorden: Quoted by Nonne.
21. Rothmann, M.: Die primären combinierten Strangerkrankungen des Rückenmarks. Deutsch. Ztschr. f. Nervenkr., 1895, vii, 171.
22. Taylor, J.: Nervous symptoms and morbid changes in the spinal cord in certain cases of profound anemia. Med. Chir. Trans., London, 1895, lxxviii, 151.
23. Teichmüller, W.: Ein Beitrag zur Kenntniss der im Verlaufe der perniciösen Anämie beobachteten spinal Erkrankungen. Deutsch. Ztschr. f. Nervenh., 1895–1896, viii, 385.
24. Von Voss, G.: Anatomische und Experimentelle Untersuchungen über die Rückenmarks veränderungen bei Anämie. Deutsch. Arch. f. klin. Med., 1897, lviii, 489.
25. White, W. H.: A clinical lecture on a case of pernicious anemia, having changes in the spinal cord. Brit. Med. Jour., 1910, i, 1393–1395.
26. Woltmann, H. W.: Brain changes associated with pernicious anemia. Arch. Int. Med., 1918, xxi, 791–836.

SENSITIZATION AND TREATMENT OF BRONCHIAL ASTHMATICS WITH POLLENS.

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In a recent paper, "A Clinical Study of 400 Patients with Bronchial Asthma,"[1] it was shown to what proteins the patients were sensitive

[1] Boston Med. and Surg. Jour., 1918, clxxix, 288.

and also that such proteins were derived from four chief sources, namely, animal hair, food, bacteria and pollens. In two other more recent papers, "The Treatment of Bronchial Asthma with Proteins,"[2] and "The Treatment of Bronchial Asthma with Vaccines,"[3] three of the chief sources of proteins which cause bronchial asthma were discussed; the former paper discussed sensitization and treatment with the proteins found in animal hair and in food and the latter paper concerned bacteria. The present paper concerns the remaining chief source of proteins, namely, pollens.

This paper will discuss in succession the treatment with pollens "preceding the pollen season," and "during the pollen season," pollens as a possible cause of continuous asthma, the specificity of proteins in the treatment of bronchial asthma in conjunction with multiple sensitization, the association of hay fever with bronchial asthma and the kind of pollens with their respective seasons that are the cause of bronchial asthma.

The method of obtaining pollen from the flower has been outlined in Study XI,[4] and the technic of the skin or cutaneous test which was used to demonstrate sensitization to the pollens has been repeatedly described. Before a patient can be treated with the pollen it is necessary to know how sensitive that patient is to the pollen, therefore different strengths of solutions of the pollen protein are used. These solutions are made as follows: To 0.5 gram of the dry pollen is added 44 c.c. of sterile normal saline and the mixture is shaken thoroughly at frequent intervals for twenty-four hours, after which enough absolute alcohol (6 c.c.) is added to the mixture to make the alcohol content 12 per cent. Again, the mixture is thoroughly shaken at frequent intervals for twenty-four hours, after which the mixture is centrifugalized at high speed and the supernatant fluid is pipetted off and saved. This supernatant fluid therefore consists of the pollen protein dissolved in a 12 per cent. alcoholic-normal saline solution and it represents, by weight, 1 part pollen to 100 parts solvent. This 1 to 100 solution is used as stock and from it other dilutions, 1 to 500, 1 to 1000, 1 to 5000 and 1 to 10,000 are made. These solutions are used for the skin tests and for treatment, and with the addition of a small crystal of thymol they keep for many months in a cool place.

The method of treating with the pollen extracts follows. The first treatment consists of 0.1 to 0.2 c.c. of that dilution next higher than the one which gave a positive skin test, or, in other words, the first dose is 0.1 c.c. or 0.2 c.c. of the strongest dilution which failed to give any skin reaction whatever, no matter how slight. With our pollen extracts the majority of patients whom we treated gave a more or less positive reaction with the 1 to 5000 dilution, therefore the

[2] Arch. Int. Med., 1918, xxii, 466.
[3] Ibid, 1919.
[4] Study XI, Jour. Med. Res., 1917, xxxvi, 237.

first treatment consisted of 0.1 c.c. or 0.2 c.c. of the 1 to 10000 dilution. Treatments were given subcutaneously once a week, and each week the amount of the extract was gradually increased, so that as the treatment progressed, stronger and stronger dilutions were used until one or more doses of the 1 to 100 dilution were given. As an example we will give what we have found by experimentation to be the best outline of treatment for a patient who gives a more or less positive skin test with a 1 to 5000 dilution of pollen extract, and then we will show how we determined upon this outline: 1 to 10000 give 0.2 c.c., 1 to 5000 give 0.2 c.c., 0.3 c.c., 0.4 c.c., 1 to 1000 give 0.2 c.c., 0.3 c.c., 1 to 500 give 0.2 c.c., 0.3 c.c., 0.4 c.c., 1 to 100 give 0.1 c.c., 0.2 c.c., 0.3 c.c., each dose to be given preferably at weekly intervals and never oftener than every five days.

Pollen Treatment Preceding the Season. By treatment preceding the season is meant that the series of treatments is completed before the season of pollination for that particular plant begins.

For instance, pollination of the plants timothy and redtop, which are the chief causes of early summer pollen asthma, takes place during June and July, so that for these particular plants, treatment must be stopped about the end of May in order to be preseasonal. The most frequent types of summer pollen asthma begin about the middle of August and continue until the first frost, which usually is early in October; this season represents the pollination of the plant ragweed, and it is the ragweed pollen that causes practically all of the pollen asthma at this season. Therefore, treatment with ragweed pollen preceding the season means that treatment must be completed not later than the middle of August.

Thirty-one patients with summer pollen asthma were treated preceding the season. Since in 3 cases the pollens timothy and redtop were the cause of asthma and in the remaining 28 cases the pollen of ragweed was the cause of asthma, treatment with the first 3 cases ceased the end of May, and with the 28 cases treatment ceased just previous to the middle of August; in each group of cases treatment was stopped for all cases at the same time.

Since all patients in each respective group did not present themselves for treatment at the same time the patients varied in the number of treatments they were given, and this variation concerned the stronger strengths of the pollen extract. This was the case because practically all the patients were more or less sensitive to the pollen in a dilution of 1 to 5000, and consequently, with practically all patients, the first treatment was 0.2 c.c. of a dilution of 1 to 10000. Therefore, the chief variation in treatment among the cases was in the number of times the smaller dilutions were given or, in other words, the patients varied in the number of doses of the 1 to 100 and 1 to 500 dilutions which they received.

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The following table clearly shows the results of varying the number of treatments with the strong solutions of the pollens:

TABLE I.

Patients.	Last few treatments.	Final dilution of pollen extract.	Results.
4	3	1 to 100	No asthma.
7	2	1 to 100	No asthma.
3	1	1 to 100	2 had no asthma, 1 not benefited.
8	3 to 5	1 to 500	5 had no asthma, 1 not benefited, 2 had slight asthma.
5	2	1 to 500	3 had no asthma, 1 not benefited, 1 had slight asthma.
4	1	1 to 500	2 had some asthma, 1 had considerable, 1 not benefited.

In the above table it is noted that all those patients who had two or three treatments with the 1 to 100 solution of pollen were entirely free from asthma during the ensuing season. Of the 3 patients who were given only one treatment with the 1 to 100 dilution, 2 were free from asthma and 1 was not benefited. Of the 13 patients who were given from two to five treatments with the 1 to 500 dilution, only 8 were entirely free from asthma, 3 others had slight asthma and 2 were not benefited. Whereas none of the 4 patients who were given only one treatment with 1 to 500 dilution were entirely free from asthma; although only 1 was not benefited, 2 had "some" asthma and 1 had considerable asthma. Therefore, it is quite evident that in order to prevent asthma caused by pollens by treatment preceding the season, two or three treatments with the 1 to 100 dilution should be given. And although two or more treatments with the 1 to 500 dilution prevented asthma in the majority of cases, the results are so much better when two or three additional treatments are given that the aim should be to continue treatment until two or three doses of the 1 to 100 dilution are given. Patients who received treatment with dilutions no stronger than 1 to 1000 are not shown in the table, because so little treatment is not worth doing.

Since it is evident that two or three treatments with the 1 to 100 dilution are necessary in order to surely protect the patient from having asthma, and since, as already stated, the majority of the patients are more or less sensitive to our 1 to 5000 dilution of the pollens, thus making it necessary to give 0.2 c.c. of a 1 to 10000 dilution of the pollen for the first dose, one must allow for at least twelve treatments as follows: 1 to 10000 give 0.2 c.c., 1 to 5000 give 0.2 c.c., 0.3 c.c., 0.4 c.c., 1 to 1000 give 0.2 c.c., 0.3 c.c., 1 to 500 give 0.2 c.c., 0.3 c.c., 0.4 c.c., 1 to 100 give 0.1 c.c., 0.2 c.c., 0.3 c.c. If the weekly interval between treatments is used it is thus necessary, in the case of the June and July asthma which is caused by redtop and timothy, to begin treatment the middle of March, and in the middle of August

to October type of asthma, which is due to ragweed, it is necessary to begin treatment the first of May.

One might ask if the results would not be as satisfactory if instead of giving a few treatments with each dilution, including the 1 to 100, a large number of treatments were given with the weaker dilution and a fewer number with the stronger dilution. In order to answer this question we will consider three patients in the above table who were not benefited by treatment. One patient was given a total of ten treatments as follows: 1 to 5000, 0.1 c.c., 0.1 c.c., 0.2 c.c., 0.2 c.c., 0.3 c.c., 0.3 c.c., 0.4 c.c., 1 to 1000, 0.1 c.c., 0.2 c.c., 1 to 500, 0.1 c.c.; another was given a total of eleven treatments as follows: 1 to 10000, 0.1 c.c., 0.1 c.c., 0.2 c.c., 1 to 5000, 0.1 c.c., 0.2 c.c., 0.2 c.c., 0.3 c.c., 0.4 c.c., 1 to 1000, 0.2 c.c., 1 to 500, 0. 2 c.c., 0. 3 c.c., and the third patient was given a total of fourteen treatments as follows: 1 to 10000, 0.1 c.c., 1 to 5000, 0.1 c.c., 0.2 c.c., 0.2 c.c., 0.3 c.c., 0.4 c.c., 1 to 1000, 0.1 c.c., 0.2 c.c., 0.2 c.c., 0.2 c.c., 1 to 500, 0.1 c.c., 0.1 c.c., 0.2 c.c., 0.3 c.c. It is thus seen that a large number of treatments with the high dilutions of the pollen and few or no treatments with the strong dilution are not beneficial. The above 3 cases, however, had to be treated as outlined because each time the dose was increased the patients had soreness at the site of inoculation, thus necessitating the repetition of each dose one or more times. Naturally as such oversensitive cases cannot be foreseen, this is another reason for starting treatment with all cases in plenty of time to allow for such delays.

After the completion of a series of treatments as outlined above, the cutaneous test with the pollens with which treatment has been given is greatly reduced in positiveness. Patients who previous to treatment gave a positive skin test with a 1 to 5000 dilution of pollen protein, give after the completion of treatment a positive skin test with dilutions of the pollen protein no higher than 1 to 100, and the skin test is even less positive than that if several treatments with the 1 to 100 dilution are given. A year later, however, these same patients give practically the same degree of positiveness with the skin test as they did previous to treatment the preceding year. Therefore, the patients become resensitized during the long interval between pollen seasons. This is as one would anticipate, because the patients are not absolutely desensitized; much more treatment would be necessary to absolutely desensitize, consequently the patients prefer to repeat the shorter series of treatments each year.

Pollen Treatment during the Pollination Season. Although, as already outlined, considerable caution must be exercised in the treatment of bronchial asthma due to pollens preceding the season of pollination, in order to avoid shocking the patient from an overdose of pollen, the danger of producing such a result is not great because the patient is not being exposed at the time of treatment to pollens in nature. Treatment with pollens, however, during the

season of pollination must be carried out with the greatest care, since during such treatment the patient is not only being injected with the pollen, but he is at the same time also being exposed to the pollens in nature. Thus there are two chances of erring: the one, the liability of not giving enough pollen to do any good, and the other, by far the more dangerous, the liability of giving too large a dose; not so much that the injected amount alone is too large as that the injected amount, together with the unknown amount which the patient is liable to encounter in nature, may be too large and thus disturbing results may follow the combination. In this method of treatment the skin or cutaneous test is very important and the correct interpretation of the test as regards the proper treatment is most important. The two following cases will illustrate both proper and improper treatment in the same individual.

Case I gave a slightly positive cutaneous test with a 1 to 1000 solution of ragweed pollen. Following a subcutaneous injection of 0.1 c.c. of the 1 to 1000 solution, he was much worse; but a week later following 0.1 c.c. of a 1 to 5000 solution, he was much better —in fact, practically relieved of asthma.

Case II was slightly sensitive by the cutaneous test to a 1 to 1000 solution of timothy pollen. Following a subcutaneous injection of 0.1 c.c. of the 1 to 1000 solution he was so much worse that he refused further treatment for the time being. However, when his asthma returned a month later, it now being caused by ragweed, to which he gave a slightly positive cutaneous test in a dilution of 1 to 5000, a subcutaneous injection of 0.1 c.c. of a 1 to 10000 dilution of ragweed pollen relieved his asthma for several days.

It is thus seen that during the pollen season treatment must be begun with such an amount that fails to give any reaction whatsoever on the skin, and yet if too small an amount is given there will be no benefit. A better testimonial than the above for the value of the skin or cutaneous test as regards the determination of the cause and the treatment of bronchial asthma could not be asked for.

Ten patients who received a sufficient number of treatments during the pollen season, and also were under observation long enough during the pollen season to justify definite conclusions, are presented in Table II.

In Table II it is noted that the first patient, F. L., who was sensitive to ragweed pollen, the second, M. F. M., who was sensitive to both timothy and redtop pollens, and the third, R. S., who was sensitive to timothy pollen alone, were all relieved of asthma by "during the season" treatment with the respective pollens to which they were sensitive. The first and second patients were better following the first dose, and they became free from asthma after the second dose, and the third patient became free after the first dose, and all three continued to be free from asthma throughout the remainder of the season, which varied between four and six weeks. The next two patients, R. H. and M. M., although not entirely

relieved from asthma, had only an occasional slight attack after treatment was begun, and as each patient was treated seven times in seven weeks, they went through practically their whole pollen season with very little trouble. The remaining 5 patients who were treated from four to seven times were not benefited at all; in other words, their asthma continued as usual in spite of treatment. Therefore, of the 10 patients, all of whom were treated exactly alike and very cautiously, 3 were relieved of asthma, 2 were greatly benefited and 5 were not benefited at all by "during the season" treatment. On comparing these results with those obtained by "preceding the season" treatment, as shown in Table I, it is evident that much greater success is obtained by treatment preceding the season than by treatment during the season. Nevertheless, if the former cannot be done the latter is worth trying.

TABLE II.

Patient.	Cutaneous test.	Treatment during season.	Result.
F. L.	Ragweed, 1 to 1000±	1 to 5000 = 0.1 c.c., 0.2 c.c., 0.3 c.c., 0.4 c.c.	Relieved.
M. F. M.	Timothy and redtop, 1 to 500+	1 to 1000 = 0.1 c.c., 0.2 c.c., 0.3 c.c.	Relieved.
R. S.	Timothy, 1 to 500+	1 to 1000 = 0.1 c.c., 0.2 c.c. 1 to 500 = 0.1 c.c., 0.15 c.c.	Relieved.
R. H.	Ragweed, 1 to 10000±	1 to 20000 = 0.1 c.c.; 1 to 10000 = 0.1 c.c., 0.2 c.c. 1 to 5000 = 0.1 c.c., 0.2 c.c., 0.3 c.c., 0.4 c.c.	Slight asthma.
M. M.	Ragweed, 1 to 1000±	1 to 5000 = 0.1 c.c.; 1 to 1000 = 0.1 c.c., 0.15 c.c., 0.2 c.c., 0.25 c.c., 0.3 c.c., 0.4 c.c.	Slight attacks.
S. R. S.	Ragweed, 1 to 5000+	1 to 10000 = 0.1 c.c.; 1 to 5000 = 0.1 c.c., 0.2 c.c., 0.3 c.c.	No benefit.
W. S. T.	Ragweed, 1 to 1000+	1 to 5000 = 0.1 c.c., 0.2 c.c., 0.3 c.c. 1 to 1000 = 0.1 c.c., 0.2 c.c.	No benefit.
T. S. R.	Timothy, 1 to 10000±	1 to 20000 = 0.1 c.c.; 1 to 10000 = 0.1 c.c., 0.2 c.c. 1 to 5000 = 0.1 c.c., 0.2 c.c., 0.3 c.c. 1 to 1000 = 0.1 c.c.	No benefit.
F. G. K.	Timothy and redtop, 1 to 500+	1 to 1000 = 0.1 c.c., 0.2 c.c.; 1 to 500 = 0.1 c.c., 0.2 c.c.	No benefit.
S. M. V.	Timothy, 1 to 1000±	1 to 5000 = 0.1 c.c., 0.2 c.c., 0.3 c.c. 1 to 1000 = 0.1 c.c., 0.2 c.c.	No benefit.

The question now arises: Should both methods of treatment be employed in the same patient provided the treatment preceding the season fails? The answer is in the affirmative, as shown by the following 2 cases who were a part of Table I. One of these patients was not benefited by four treatments with the 1 to 500 dilution of the pollen (see Table I); his asthma began at the usual time, so that treatment "during the season" was then tried. He was given at weekly intervals ragweed pollen in a dilution of 1 to 10000, 0.1 c.c., 0.2 c.c., 0.3 c.c., then 1 to 5000, 0.2 c.c., and 0.2 c.c.; after the third treatment he became free from asthma and continued to be

free through the remainder of the season. The other patient who was not benefited by one treatment of the 1 to 100 dilution (see Table I) preceding the season was given a 1 to 5000 dilution 0.1 c.c., 0.2 c.c., 0.3 c.c., 0.4 c.c., at weekly intervals during the season. For five days following each treatment he was free from asthma, but for the succeeding two days of each interval he had asthma as usual. It should be noted that although both patients had had a number of treatments preceding the season, including the dilutions of 1 to 5000, 1 to 1000 and 1 to 500, when treatment was continued during the season the dose or amount of each treatment was dropped back to that which was first used, namely, 1 to 10000 in the first case and 1 to 5000 in the second case. In other words, they were treated during the season just as though they had not been treated preceding the season. One might ask why this was necessary and why not continue throughout the season, gradually increasing the dose from where the treatment preceding the season left off? The following case (and others might be cited) will show that it is not advisable to give a few treatments preceding the season and then continue increasing the dose through the season. This patient, who was given one treatment of the 1 to 500 dilution and not benefited (see Table I), was continuously treated with gradually increasing amounts throughout the season, with no benefit, and probably the patient had worse asthma than usual. Therefore, a few treatments preceding the season is not advisable. This is probably because the patient is getting large amounts of the pollen in the treatment and at the same time is getting considerable pollen from natural sources, and the combination of the two is sufficient to overcome whatever desensitization has been accomplished by the treatment given preceding the season.

Therefore, in the treatment of pollen asthma there are only two methods available: the best method is to give sufficient treatment preceding the season of pollination and then stop, and by sufficient treatment is meant to begin treatment three months ahead of the season, so that the few final treatments will be with the strongest dilution of the pollen protein (that is, our 1 to 100 dilution). If this method happens to fail, treatment may be continued through the season, but the dosage must not continue on the increase from the amount last given; the dosage must be dropped back to the original first dose and very cautiously increased. The only other method worth doing is not to give any treatment preceding the season but wait until the patient begins to have asthma, then treat cautiously; first give one or more doses of the highest dilution which fails to give any reaction whatsoever on the skin and very slowly increase the succeeding doses. It is far better to give two doses that are so small that no improvement results before a beneficial amount is given than to run the risk of giving too large an initial dose, which may upset the patient and thus discourage the physician.

Pollens as a Possible Cause of Continuous Asthma. Frequently, patients who have asthma more or less continuously throughout the year give a history of onset of asthma or of their first attack during some summer month when some flowers are pollinating, and they also give a positive cutaneous test with the pollens of that particular season. Frequently the relationship between pollens and continuous asthma is even more suspicious; each year the patient begins asthma during a pollen season, but the asthma does not stop when the season of pollination is over; instead the asthmatic condition persists for several months or until the first seasonable spring weather the following year. Such a patient will then be well until that particular pollen season occurs again; the patient is sensitive to the pollens occurring during that season. The following case well illustrates the sequence of events in this type of asthma. The patient has had hay fever and asthma for nineteen years, and she gives a positive cutaneous test with ragweed pollen in a dilution of 1 to 5000. During the first few years the patient had hay fever and asthma from the middle of August to the first of October, thus being at that time a typical ragweed pollen case. A few years later the asthmatic condition would continue until December, although the hay fever would stop as usual in October. A few years later still the asthmatic condition continued until spring, the hay fever still ceasing as usual. During the past two years the asthmatic condition has continued the year round, although she only has hay fever as usual from the middle of August to the first of October. Other cases in whom the pollens are less suspiciously a cause of continuous asthma give a history that their asthma, although continuous throughout the year, is much worse during certain summer months, and they give positive skin tests with the pollens which are prevalent at that particular time.

Table III includes 14 cases which are instances of the above, and in 7 of these the relief from asthma following treatment with the pollens confirms the belief that pollens were the primary cause of asthma.

TABLE III.

Patient.	Onset.	Positive skin test with pollens.	Duration.
1. Miss B.	July	Timothy, redtop and ragweed	Throughout year.
2. Miss L.	July	Timothy, redtop and ragweed	Throughout year.
3. Mrs. G.	August	Ragweed	Throughout year.
4. Mr. T.	August	Ragweed	Throughout year.
5. Miss W.	August	Ragweed	Throughout year.
6. Mr. G.	August	Ragweed	Throughout winter.
7. Mr. F.	August	Ragweed	Through November
8. Mrs. M.	August	Ragweed	Throughout winter.
9. Mr. S.	August	Ragweed	To December.
10. Mr. P.	August	Ragweed	To December.
11. Mr. A.	August	Ragweed	To November.
12. Mrs. S.	August	Ragweed	To November.
13. Mrs. O'L.	August	Ragweed	Throughout winter.
14. Mrs. M.	August	Ragweed	Throughout winter.

The above group of cases needs little explanation. The first 2 patients began to have asthma in July; they were sensitive to the summer pollens—one was always worse in summer—and, although the asthma continued throughout the year, pollens were suspected as the primary cause of the asthma. The next 3 patients are similar to the first 2, with the exception that the first attack of asthma occurred during August, when ragweed pollen is in season, and consequently ragweed pollen may be suspected as the primary cause of asthma. The remaining patients are similar to the 3 just discussed, with the exception that asthma did not continue all the year, but instead it stopped at various times during the winter; in the last 2 cases it is most suspicious that ragweed primarily caused asthma, since during the first few years the asthma was confined to the months of August and September, which is the season of ragweed pollination. So much for the supposition as based upon history. Fortunately we have had the opportunity through pollen treatment of confirming our belief that pollens were the primary cause of asthma in some of these cases. These treated cases will be discussed in the following paragraph:

The first patient (Miss B.) in Table III, whose asthma began in July, who has always been worse in summer and who was sensitive to the pollens of timothy, redtop and ragweed, has had two of the best summers—in fact, has had very little asthma—following a series of treatments with the pollens to which she was sensitive.

Patient No. 8 (Mrs. M.) was treated with ragweed pollen, to which she was sensitive, and following treatment she had no asthma as usual during August and September, neither has she had any asthma during the winter; previous to this she has had asthma as shown in Table III for over thirty years.

Patient No. 9 (Mr. S.), who has had asthma for five years, from the middle of August to December, and was sensitive to ragweed pollen, had no asthma at all for two years following a series of ragweed treatments given each year for these two years; the next year no ragweed treatment was given, and he had asthma as usual.

The remaining five patients (Nos. 10, 11, 12, 13, 14) were all quite similar in that they all had had asthma for years from August to or through the winter months; they were all sensitive to ragweed pollen, and following ragweed treatment they all were entirely free from asthma during the ensuing fall and winter. Therefore, these 8 patients who were free from asthma following treatment with the pollens to which they were sensitive would seem to definitely establish the fact that pollens were the primary cause of asthma in such cases, and that surely such patients should be treated with the pollens to which they are sensitive on the chance that they may be relieved of asthma.

The question now arises, Why does not the asthma in such cases stop when the pollen season terminates, or, in other words, what

prolongs the asthma after the primary cause ceases to exist? The answer is that various other causes prolong the asthma, and one of these is bacteria as a secondary invader. Six to eight weeks of continuous severe asthma may cause so much local irritation in the bronchial tree that the field is fertile for secondary bacterial invasion, and in addition the patient's general resistance has been lowered. In Table III, Cases No. 6 (Mr. G.), No. 9 (Mr. S.) and No. 12 (Mrs. S.) represent such an instance. Case No. 6 was not treated with pollen, but after the pollen season was over treatment was begun with his autogenous sputum vaccine, and he gradually became free from asthma until entirely so after three or four doses; this same procedure was repeated a second season, with the same good results, although for the previous seven years without treatment the asthma continued all winter. Cases Nos. 9 and 12 were similarly treated, with equally good results, the year preceding that in which pollen treatment was given.

TABLE IV.—SPECIFICITY OF PROTEINS IN THE TREATMENT OF BRONCHIAL ASTHMA.

Patient.	Duration of asthma.	Positive skin test.	Treatment and remarks.
1. M. A.	August to October	Ragweed	Vaccine no benefit; ragweed pollen relieved.
2. H. B.	June to July	Pollens slight	Pollens no benefit; vaccines relieved.
3. A. G.	Throughout year	Ragweed slight	Ragweed no benefit; vaccines relieved.
4. D. M.	Throughout year	Ragweed slight	Ragweed no benefit; vaccines relieved.
5. J. M.	Throughout year	Ragweed	Ragweed relieved in summer; vaccines relieved in winter.
6. R. S.	Throughout year	Early and late pollens	Pollens relieved in summer; vaccines benefited in winter.
7. I. G.	Throughout year	Ragweed, S.P. albus	Ragweed relieved in summer; vaccines of S.P. albus relieved in winter.
8. R. W.	Throughout year	Timothy: horsehair	Timothy relieved in summer; horsehair proteins relieved in winter.
9. C. S.	Throughout year	Timothy: horsehair	Timothy relieved in summer; horsehair proteins relieved in winter.
10. W. G. T.	Throughout year	Ragweed: horsehair	Ragweed relieved in summer; horsehair proteins relieved in winter.
11. M. M.	Throughout year	Redtop; timothy; horsehair	Pollens relieved in summer; horsehair proteins relieved in winter.
12. M. P.	Throughout year	Ragweed	Ragweed relieved the complication of hay fever but asthma not benefited.

Other causes which may prolong a pollen asthma, or, in other words, other causes which together with pollens produce a more or less continuous asthma, are included in Table IV under the title,

The above group of cases needs little explanation. The first 2 patients began to have asthma in July; they were sensitive to the summer pollens—one was always worse in summer—and, although the asthma continued throughout the year, pollens were suspected as the primary cause of the asthma. The next 3 patients are similar to the first 2, with the exception that the first attack of asthma occurred during August, when ragweed pollen is in season, and consequently ragweed pollen may be suspected as the primary cause of asthma. The remaining patients are similar to the 3 just discussed, with the exception that asthma did not continue all the year, but instead it stopped at various times during the winter; in the last 2 cases it is most suspicious that ragweed primarily caused asthma, since during the first few years the asthma was confined to the months of August and September, which is the season of ragweed pollination. So much for the supposition as based upon history. Fortunately we have had the opportunity through pollen treatment of confirming our belief that pollens were the primary cause of asthma in some of these cases. These treated cases will be discussed in the following paragraph:

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5. J. M.	Throughout year	Ragweed	Ragweed relieved in summer; vaccines relieved in winter.
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Other causes which may prolong a pollen asthma, or, in other words, other causes which together with pollens produce a more or less continuous asthma, are included in Table IV under the title,

Specificity of Proteins. We have shown in previous papers that in the treatment of bronchial asthma there is a specificity of proteins, but pollens have not been included in this connection; also, the question of multiple sensitization or multiple causes of asthma in the same individual has been discussed without particular reference to the pollens. Therefore, although the chief reason for presenting Table IV is to illustrate the specificity of proteins in the treatment of bronchial asthma, the cases also illustrate multiple sensitization and various causes for the prolongation of pollen asthmas.

In Table IV the first patient (M. A.) who had asthma during the ragweed pollen season and who was sensitive to this pollen has been under observation three years. The first year treatment with a vaccine of Staphylococcus pyogenes aureus, while he was having asthma, had no effect on his condition; the next year he was treated, preceding the season, with ragweed pollen, and he had no asthma; last year he was not treated at all and he had asthma as usual. The second patient (H. B.), who had had asthma for five years only during June and July, and was only slightly sensitive to the pollens corresponding to that season, was not benefited one year by treatment either preceding or during the season with those pollens, but the next two seasons he was relieved by autogenous sputum vaccines. The next two patients (A. G. and D. M.) are so similar that they may be considered together. Both patients, who had had asthma for seven years continuously throughout the year and were only slightly sensitive to ragweed pollen, were treated preceding and during the season with ragweed pollen without benefit; treatment, however, with autogenous sputum vaccines relieved the asthma in both cases and they remained free from it while under vaccine treatment, which has been given to them off and on for the past two years. Therefore, these 4 cases illustrate the specificity of proteins in the treatment of bronchial asthma; the first case was strongly sensitive to ragweed pollen, and treatment with it prevented asthma (specific treatment); however, treatment with vaccines did not benefit (non-specific treatment); the remaining 3 cases were so very slightly sensitive to pollens that pollen treatment was not indicated, therefore the pollen treatment which these patients were given was non-specific and not beneficial; following vaccine treatment, however, these patients were relieved. The latter 3 patients bring up the question how strongly positive must be a reaction to pollens to indicate pollen treatment; this will be discussed later on in this paper.

The next 2 cases in Table IV, namely, J. M. and R. S., may be considered together. Both were positive with pollens and pollen treatment preceding the season prevented both from having asthma during the pollen season; nevertheless, their asthma returned during the winter. Treatment with autogenous sputum vaccines, however, relieved one patient entirely of asthma; the other patient was

greatly benefited. These 2 cases definitely show the specificity of treatment, and like those patients presented in Table III, they illustrate the importance of pollen treatment in those patients who are definitely sensitive to pollens even though such patients have asthma after the pollen season is at an end.

The next five patients in Table IV, namely, I. G., R. W., C. S., W. G. T. and M. M., are similar. All were sensitive to pollens, and pollen treatment prevented asthma during the pollen seasons; but during the remainder of the year they had asthma as usual. These patients were, however, sensitive to other proteins—Case I. G. to Staphylococcus pyogenes albus and the other patients were sensitive to the proteins of horse dandruff, and treatment with these proteins relieved and prevented the winter asthma which they had been having for periods varying between eight and seventeen years. These patients not only illustrate the specificity of proteins in the treatment of bronchial asthma, but also multiple sensitization and the necessity of treatment with more than one type of protein in such cases; furthermore, such cases confirm the value of the skin or cutaneous test.

The last case (M. P.), in Table IV, had asthma throughout the year and hay fever from the middle of August to the first frost; she was sensitive to ragweed pollen. Treatment with ragweed pollen preceding the season prevented her from having her customary fall hay fever, but her asthma was the same as usual. Therefore, the pollen treatment explained the cause of hay fever but not the cause of asthma, and thus the patient had two separate conditions from different causes at the same time. This is another instance of specific protein treatment, of the specific value of the cutaneous test and of the necessity of treatment as determined by the skin test, in order to rule out all possible causes of brochial asthma. This case also brings up the association of hay fever with brochial asthma.

Association of Hay Fever with Bronchial Asthma. In this paper have been included only those patients who had bronchial asthma throughout the whole or greater part of the respective pollen season. For instance, many such patients had asthma throughout the season, many others had asthma after a few days of hay fever, then both continued throughout the season and the remainder had hay fever for ten days to two weeks before asthma began, then both continued throughout the season. Frequently, hay fever patients have a very slight attack of asthma at some time during their hay fever, often the hay fever symptoms end with a day or two of asthma and still others are more or less choked up at times during their hay fever. None of the latter cases are included in this paper because the amount of asthma was too slight and the attacks too unreliable to claim benefit or relief from treatment. These cases do, however, show the frequent association of hay fever and asthma when caused by pollens.

Of the 31 patients in Table I who were treated preceding the season, 27, or all but 4, had hay fever with their asthma; of the 10 patients in Table II who were treated during the season, 7, or all but 3, had hay fever with their asthma; and two other similar typical pollen asthmas, who were presented in this paper, to show the necessity of carefully selecting the proper dose of pollen, also had hay fever with their asthma. Therefore, of the typical pollen asthmatics, in 80 per cent. hay fever was associated with asthma and both conditions were caused by the same pollen as shown by pollen treatment.

Among the 14 patients in Table III there were 8 who also had hay fever, and of the 10 patients in Table IV who had asthma throughout the year 2 had hay fever. In the whole series of 600 asthmatics, excluding those who are included in this paper, there were 12 who had hay fever. Therefore, a positive cutaneous test with pollens in patients who have bronchial asthma may mean that those patients have pollen hay fever and that the pollens play no part in the cause of asthma; the only way to tell is to treat with the pollens which give positive tests.

Eleven patients who had bronchial asthma and who are not included in this paper gave positive cutaneous tests with pollens in dilution no stronger than 1 to 500; 5 of these gave a positive test in a 1 to 100 dilution and the remaining 6 patients gave positive tests with the 1 to 500 dilution. As a general rule it seems unnecessary to treat such cases with pollens, especially if the patients are sensitive to other proteins, because in the experience we have already outlined they are probably not sufficiently sensitive to pollens to have much trouble from them. In the last four paragraphs entitled "The Asssociation of Hay Fever with Bronchial Asthma," the 92 patients who, in a former paper,[5] were shown to be sensitive to pollens have thus all been accounted for.

The Pollen Seasons and the Pollens That Cause Bronchial Asthma. There are three definite pollen seasons. The first occurs in April and May when the various trees pollinate; among the first to pollinate during this season are the willow, birch and maple and the last one to pollinate is the pine, which occurs the last day or two in May. Although the pollen of any of these trees may cause asthma, we have had only one case caused by willow, one by birch and one by pine pollen. Since the length of time which each tree requires to complete pollination is no longer than two weeks, and in the case of the pine tree only one day, it is quite unnecessary to treat these patients for such a short exposure to the pollen.

The second pollen season, and a more important one, occurs during June and July. The principal plants which pollinate at this time are the rose, June grass, orchard grass, redtop and timothy;

[5] Boston Med. and Surg. Jour., 1918, clxxix, 288.

the latter two are also grasses and are familiarly known as hay. We have not had a case of asthma caused by the rose, although there are such on record; neither have we found orchard grass to be a cause; these two plants surely are not frequently a cause of asthma. June grass is so similar botanically to redtop that we do not use it in our tests. The important plants in this group are redtop and timothy grasses, and of these two timothy is the chief cause of bronchial asthma at this season. Practically every patient who was sensitive to timothy was also somewhat sensitive to redtop, but usually less so. In our series of cases redtop never gave a stronger reaction than timothy; in only 5 cases did both pollens give an equally strong reaction and in only 1 other case did redtop give a test nearly as strong as did timothy; in the 8 remaining cases included in this paper redtop reacted little or not at all, while timothy gave a strong reaction. (The adjectives qualifying reaction refer to various dilutions of the pollen protein; for instance, an equally strong reaction means that both pollens gave a positive test in the same high dilutions, and referring to the latter part of the previous sentence concerning the 8 remaining cases it is meant that these cases gave a positive skin test with high dilutions of timothy, whereas with redtop the patients either gave negative tests or positive tests with only very low dilutions.) Patients who were equally sensitive, or nearly so, were treated with both pollens, but those who gave positive tests with high dilutions of timothy and with concentrated dilutions of redtop were treated only with timothy pollen extract. A fair idea may be obtained regarding the frequency of these pollens as a cause of asthma by referring to Tables I and II, which included definite cases of seasonal pollen asthma; of the total of 41 cases, in 8 the pollens of redtop and timothy were the cause of asthma; this percentage of frequency, however, is a little too high for a large series of cases.

The third pollen season, and by far the most important, occurs during August and September, and the important pollens at this time are those of ragweed, golden rod and daisy. The daisy really begins to pollinate in July and finishes in early September; golden rod pollinates during August and September and ragweed usually begins to pollinate about the middle of August and ceases with the first heavy frost, which usually occurs early in October. Ragweed is practically always the cause of pollen asthma at this season, and in only one case have we found the daisy the cause, and in one other was golden rod the cause. These three plants belong to the same botanical family, although they are not intimately related to each other, and consequently every patient that reacts positively to one need not react to all. The proportion of positive skin reactions among these three pollens is brought out by the patients presented in Tables I and II. Of the 41 patients presented in the two tables, in 32 the asthma was caused by ragweed pollen alone and in one

other both ragweed and daisy pollens were the cause. This shows how much more frequently ragweed pollen causes bronchial asthma than the next most common pollens that cause it, namely, redtop and timothy. Of the 32 patients who had asthma from ragweed pollen, 3 gave a positive cutaneous test with ragweed pollen protein in a dilution of 1 to 10000, 21 with a dilution of 1 to 5000 and 8 were positive with a dilution no stronger than 1 to 1000. These same patients gave skin tests with the pollens of the daisy and golden rod as follows: 6 were negative with the whole pollen of golden rod and 5 with the whole pollen of the daisy, 5 were positive with the whole pollen of golden rod but negative with a 1 to 100 dilution, and with the whole pollen of the daisy one was positive, 13 were negative with golden rod diluted 1 to 100, but whole pollen was not tested and 15 were negative with the daisy diluted 1 to 100, but whole pollen was not tested; 7 other patients were positive with golden rod pollen extract in a dilution of 1 to 100 but negative with higher dilutions, and 6 were positive with the daisy pollen extract diluted 1 to 100 but negative with high dilutions; 2 patients were positive with golden-rod pollen in a 1 to 500 dilution and 3 were positive with daisy 1 to 500; no patients were positive with golden-rod pollen extract in dilutions higher than 1 to 500, whereas with daisy pollen extract 2 were positive with 1 to 1000 dilution and one with 1 to 5000 dilution. Since the above patients were treated only with ragweed pollen, to which they were most sensitive, with the exception of the one patient who was equally sensitive to both ragweed and the daisy and was treated with both, it is evident that in practically all patients who have pollen asthma during August and September ragweed is the cause.

Attention should be called to the fact that some patients have so-called asthma during June and July, others during August and September and still others have so-called asthma throughout the summer; but they are not sensitive to pollens, and the asthma in these cases is caused by bacteria; a series of these cases was reported in a previous paper.[6] Therefore, it is essential to do the skin or cutaneous test in all cases of summer asthma, and it is just as ridiculous to treat all summer asthmatics with pollens. Furthermore, it is unnecessary and possibly harmful to treat pollen asthmatics with an extract composed of many pollens, such as in the past has been put on the market by commercial firms, when the patient actually requires only one or possibly two varieties of pollen. Attention should also be called to the fact that occasionally the pollen seasons vary in time, depending upon weather conditions. For instance, during the summer of 1918 June grass pollinated in May, red top and timothy were still pollinating in August and ragweed began to pollinate the first week in August. Naturally these

[6] Arch. Int. Med., 1919.

seasons also vary with localities. What has been written in this paper holds for Massachusetts, but farther north the seasons are retarded and farther south the seasons are ahead of this schedule. Furthermore, the same pollens are not found in all localities. There are places in New Hampshire where ragweed does not grow; in Florida there is no ragweed, but golden rod grows in abundance; in the South and middle West the grass alfalfa abounds, and, as shown by Selfridge,[7] none of the eastern pollens are found in California. Therefore the ridiculousness of treating summer asthmatics over the whole country with the same pollens, as in the past some commercial houses have advocated, is quite evident and the necessity of doing skin or cutaneous tests is just as evident.

In conclusion, readers of this paper should bear in mind that we collected our own pollens and made our own preparation by the method already outlined and that our results depend upon these facts. Our results will naturally be specifically true only when our methods are followed or with those who purchase the individual pollen preparations which are comparable with our own. Otherwise, our results will hold only in a general way as regards the degree of sensitiveness of the patient and the amount of treatment necessary.

Conclusions. Patients who have seasonal bronchial asthma caused by pollens are prevented from having asthma by a series of treatments with the pollens to which they are most sensitive provided sufficient treatment is given, and by this is meant a series of treatments consisting of various dilutions of the pollen protein ranging from the strongest dilution which fails to give a positive cutaneous test to the strongest dilution which gives a positive test. When our methods are used the usual proper treatment is as follows: 1 to 10000 give 0.2 c.c., 1 to 5000 give 0.2 c.c., 0.3 c.c., 0.4 c.c., 1 to 1000 give 0.2 c.c., 0.3 c.c., 1 to 500 give 0.2 c.c., 0.3 c.c., 0.4 c.c., 1 to 100 give 0.1 c.c. 0.2 c.c., 0.3 c.c.

Treatment with pollens during the season is less reliable, but worth doing provided much treatment preceding the season fails or cannot be given. In such cases very small amounts of the pollen protein should be given.

[7] Spasmodic Vasomotor Disturbances of the Respiratory Tract, with Special Reference to Hay Fever, California State Jour. of Med., April, 1918.

Other papers on the study of bronchial asthma made possible through a gift by Mr. Charles F. Choate, Jr., of Boston, to the Peter Bent Brigham Hospital are as follows:

Studies I–V, Jour. Med. Research, 1917, xxxv, 373, 391, 487, 497, 509.
Studies VI–VIII, Jour. Immunol., 1917, ii, 227, 237, 243.
Study IX, Am. Jour. Bot. July, 1917.
Studies X–XIII, Jour. Med. Research, 1917, xxxvi, 231, 237, 243, 295.
Study XIV, ibid., xxxvi, 423.
Study XV, ibid., 1917, xxxvii, 51.
Studies XVI and XVII, ibid. 1917, xxxvii, 277, 287.
Study XVIII, Jour. Am. Med. Assn., 1918, lxx, 897.
The Cause and Treatment of Bronchial Asthma, Med. Clinics of North America, Boston, 1918, i, No. 4.

Asthma caused by pollens may continue after the termination of the pollen season. The continuation of asthma in these cases is due to secondary bacterial infection, causing bronchitis in a patient whose resistance, either local or general, has been lowered because of prolonged, severe pollen asthma.

Patients who have continuous asthma throughout the year should be treated with pollens if they give positive cutaneous tests with them, in order to determine whether or not the pollens may in part be a cause of asthma. The association of hay fever with brochial asthma is so common in pollen cases, and is sufficiently frequent in continuous asthma to warrant pollen treatment in all patients who are sensitive to pollens.

The most common pollen that causes seasonal asthma is that of ragweed, whose season of pollination extends, as a rule, from the middle of August to the first frost, or about the first of October. The next most common pollens to cause asthma are those of redtop and timothy, usually both together, but of the two, timothy is the more frequent cause. These, however, are poor seconds to ragweed pollen. The season of pollination of redtop and timothy is during June and July. Rarely the pollen of various trees which pollinate during April and May, the pollen of the rose during June and July, the pollen of the daisy during July and August and the pollens of corn and golden rod during August and September are the cause of bronchial asthma.

REVIEWS

SURGICAL TREATMENT. By JAMES PETER WARBASSE, Formerly Attending Surgeon to the Methodist Episcopal Hospital, Brooklyn, New York. Volume 1. Pp. 899; 699 illustrations. Philadelphia and London: W. B. Saunders Company, 1918.

THE author here presents the first volume of a large three-volume work on surgical treatment. Judging the prospective two volumes by this one, we recognize a very ambitious effort and one worthy of the tremendous amount of work it has required. The outstanding feature is that it is a one-man production in contrast to the usual system of surgery by many authors. The one-time common and popular text-book of surgery by one author seems to have lost its hold on the profession, with a few noteworthy exceptions. Even the large systems by many authors, most of whom work and write along special lines, do not seem to maintain their popularity through more than a few editions, evidently because they cannot keep abreast of the important advances in surgery. The progressive surgeon must be familiar with the original literature as it appears in the journals. Even in the matter of surgical treatment alone, one not infrequently fails to realize how difficult it is to condense this amount of material, or the best of it, into the narrow confines of three volumes. Whatever their defects, such books are very essential in the life of the busy surgeon for ready reference and reasonably reliable guidance, and there is much to be said for this unusual one-man system. Duplication and overlapping of subjects is largely avoided. Many noted writers on special branches of surgery have displayed much difficulty in determining what the average physician and general surgeon need most. Warbasse shows not only a remarkable capacity for absorbing the literature himself, but for presenting its essential features in such a form that the ordinary reader may absorb it also.

A striking general feature is the wide area covered with a noteworthy attention to detail. In view of the great number of surgical contributions, due to the war needs and irrespective of the war, the author displays an unusual ability to be brief, comprehensive and clear in his summaries of this material. The general excellence of the work and of the numerous illustrations make it difficult to particularize concerning individual features. The reviewer, however,

cannot agree with the author in all things. He would criticize, for instance, Fig. 215, on page 365, which shows digital pressure being made on the femoral artery about under the spine of the pubis instead of under the middle of Poupart's ligament. All surgeons will not agree that "ordinarily the reduction of a fracture is simple and satisfactory." A skiagraphic illustration of a fracture of the shafts of say both bones of the leg, with considerable overlapping of the fragments before reduction, and a similar illustration of the same fracture showing reduction of the deformity would have been more convincing. Diagrammatic illustrations do not satisfy. Compressing the artery supplying the bone, the use of drugs or of anemia by the ischemic rubber bandage, to aid the reduction by relaxing the muscles, will not appeal strongly to the experienced surgeon. That fractures of the greater tuberosity of the humerus and of the head and neck of the radius are rare is not supported by the roentgen-ray evidence. Fig. 475, on page 633, is evidently copied from one which appeared elsewhere a few years ago, and its reappearance is unfortunate. It illustrates an operation for recurrent dislocation of the shoulder that never was done and never will be, because the anatomical conditions illustrated do not exist. To the uninitiated it is alluring, but if followed will prove bitterly disappointing.

But these are trifles in a great mass of up-to-date, readily digestible, well coördinated, surgical therapeutic facts, very valuable and necessary to the practising surgeon. The author is to be congratulated on the magnitude and importance of the work he has accomplished. The surgeon and practising physician are also to be congratulated because of the opportunity it affords of finding what they need most of modern surgical knowledge so arranged and illustrated that it is readily accessible. T. T. T.

Forced Movements, Tropisms and Animal Conduct. By Jacques Loeb, Member of the Rockefeller Institute for Medical Research. Pp. 209; 42 illustrations. Philadelphia: J. B. Lippincott Company, 1918.

This is the first of a projected series of monographs on general physiology and experimental biology by American writers. It is now thirty years ago since the author of this book put forward his well-known theory of tropisms or forced movements in regard to animal behavior. The idea was first suggested to him by observing the behavior of plants, such as stems bending toward the light of a window or the growing ivy stem inclining toward a solid support. By careful experimental procedures he found the behavior of lower animals to be similarly governed by external forces. To these forces he applied the same terms as had been used in plant physi-

ology, as heliotropism, galvanotropism, geotropism, etc. In the interval since the idea was first advanced many investigators have worked upon the lines which the author then indicated. This is attested to by the 554 references to literature at the end of the book. These and the discussion of their results, which the book contains, will serve as a source of collected information and of reference to all those interested in the subject. W. H. F. A.

THE HUMAN SKELETON. AN INTERPRETATION. By HERBERT E. WALTER, Associate Professor of Biology, Brown University. Pp. 214; 174 illustrations. New York: The Macmillan Company, 1918.

To those whose early study of the human skeleton was coincident with the first strenuous months of their medical education, this simple presentation will serve to give a new viewpoint. Instead of time-honored descriptions and hackneyed expressions, the author uses every-day language in his attempt to inject life into the dry bones. Perhaps some may disapprove of his partly humorous method of handling scientific facts. His interpretation is largely based upon evolutionary lines, or, to use one of the author's own expressions, "the present skeleton is only the latest model," and is bound in the future to undergo many modifications. To show the directions in which the various parts of the skeleton are evolving, he draws largely upon comparative anatomy and embryology. The result is a readable book, in which the more general and larger aspects of the subject are emphasized to the exclusion of much of the usual minutiæ. W. H. F. A.

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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Post Malarial Severe Anemia.—HARRINGTON and WHITELAW (*Glasgow Med. Jour.*, June, 1918, No. 51) state that shortly after their arrival in Macedonia they were impressed by the occurrence after malaria of cases of grave anemia, apparently of the pernicious type. It was found possible to examine 80 cases, involving 121 full blood counts and complete physical examinations. With the exception of a few Bulgar and German prisoners the patients were all Serbian soldiers. For the differential results, five hundred cells were counted. (I) *Severe Forms:* (1) Post-malarial anemia may assume a grave type characterized by all the signs and symptoms of pernicious anemia but without evidence of oral or intestinal sepsis. (2) The spleen is enlarged, sometimes considerably so, but the liver is seldom enlarged. (3) The blood shows marked diminution of red corpuscles, high color index, leukopenia with a relative increase of lymphocytes and to a lesser extent of large mononuclears, poikilocytosis, megalocytosis, polychromasia, occasional granular basophilia, the presence of megaloblasts and normoblasts, and a small percentage of myelocytes frequently, and myeloblasts constantly. (4) Such cases occur most frequently as a sequel of subtertian malaria, but may follow benign tertian. (5) Recovery usually follows prompt and energetic treatment, but death may occur, and the gravity of the prognosis increases with the age of the patient. (6) Treatment by arsenic used as in pernicious anemia, either as liquor arsenicalis in increasing doses, or galyl or kharsivan intravenously, usually leads to recovery. It should be combined with treatment by quinine, orally or

intramuscularly as indicated. (II) *Mild Forms:* (1) The blood shows a less marked diminution of red corpuscles, a low color index except in a few more recent cases, a less marked leukopenia with a relative increase of lymphocytes, and large mononuclear cells, slight poikilocytosis, occasional megalocytes and polychromasia, rarely granular basophilia, the presence of normoblasts and rarely of megaloblasts, and a small percentage of myelocytes frequently, and of myeloblasts constantly. (2) The average age of the patients is lower. (3) Recovery is the rule.

The New Treatment for Paralysis Agitans.—SWIFT (*Boston Med. and Surg. Jour.*, November 21, 1918, No. 21, clxxix, 644) cites briefly the treatment of three typical cases of a method which consists solely in the muscular movements of a simple nature, gone through very slowly, at the rate of about one foot to the second, with strong mental concentration upon the movement while it is in progress. First come movements of the right foot, then of the left, then of the legs successively, then of the right and left arms in order, then of both arms, and finally of the hands and fingers. The object is not muscular development but rather development of nervous control over the muscles. The movements should be regular and they should be definitely prescribed, but it is not necessary to outline any special form for them in this place because they can easily be invented by anyone. No particular value need be attached to any special set of exercises, because the nervous control is the same in one as in another. It seems likely that the essence of the entire treatment lies in this slowness of movement, and perhaps also in the mental concentration which should accompany the movement. The purpose of these exercises is to develop just this feeling of pervading steadiness to such a pitch that it endures as a constant feature of the patient's physical life. By my own experience with them and by my observation of patients' use of them I am led to believe that these exercises do build up a central inhibitory control.

The Bacillus Influenzæ in Sinusitis and Meningitis.—LACY (*Jour. Lab. and Clin. Med.*, November, 1918, No. 2, iv, 55) reports case histories and postmortem pathological and bacteriological findings in two cases of influenzal meningitis in infants and the clinical and bacteriological findings in two cases of frontal sinusitis in young men. He concludes: In all cases of meningitis, either mild or severe, of indefinite etiology it is advisable to centrifuge the spinal fluid and culture it on various media, always using blood agar. Observations on this should be made for at least forty-eight hours before a negative report is made. The presence of Gram-negative bacilli in direct smears or on cultures from cerebrospinal fluid or from the accessory sinuses of the respiratory tract should be looked upon as probable Bacillus influenzæ. This is especially true when long filamentous forms are present. There are probably two types of B. influenzæ as suggested by the cases reported here: the one which retains its original short bacillary form indefinitely on artificial media and the other which readily develops filamentous forms after a few days on moist blood agar. Sinus infections with the B. influenzæ should have early and adequate drainage to prevent the danger of a complicating meningitis. *Note.*—Since the completion of the above work, Major H. E. Robertson, of the American Expedi-

tionary Force in France, has reported the recovery of B. influenzæ from the accessory sinuses of 14 cases at autopsy: 7 times out of 8, cases of influenzal tracheobronchitis; 6 times from patients dead from other infectious diseases; and 2 from men dying of accidental causes. Major Robertson did not go into the cultural characteristics nor morphological differences of the bacillus.

A Study of the Neutralization Properties of Antipoliomyelitic Horse Serum.—NUZUM (*Jour. Infect. Dis.*, September, 1918, No. 3, xxiii) says that antipoliomyelitic horse serum prepared by repeated intravenous injections of the coccus isolated from the central nervous system in human and monkey poliomyelitis possesses neutralizing properties against the virus of poliomyelitis. Immune horse serum protected 11 monkeys perfectly against fatal doses of virus. In two monkeys in which both immune human serum and immune horse serum failed to neutralize the virus, a definite delay of sixteen days in the onset of paralysis must be attributed to the immune horse serum as compared with a shorter delay of eleven days with immune human serum known to possess much neutralizing principles. The neutralizing properties of antipoliomyelitic horse serum *in vitro* for the virus of poliomyelitis afford a convenient and satisfactory test of the potency of this serum for use in the treatment of poliomyelitis. Suitable controls with normal horse serum and comparisons with immune human serums known to possess neutralizing properties should be conducted simultaneously. Finally, the neutralizing, protective and curative properties of antipoliomyelitic horse serum for experimental poliomyelitis of monkeys are in direct accord with the favorable results observed in the serum treatment of human poliomyelitis and argue strongly for the etiological relationship of the coccus to this disease.

Report of Epidemic of "Spanish Influenza" Which Occurred at Camp A. A. Humphreys, Va., during September and October, 1918, by I. W. Brewer, M.D., Geneva, N. Y., Lieutenant-Colonel, M. C., N. A., Camp Surgeon, Camp A. A. Humphreys, Va.—(*Jour. Lab. and Clin. Med.*, December, 1918, No. 3, iv, 87). In a detailed analysis of the report of the so-called "Spanish Influenza," well illustrated by graphic charts, the author analyzes the statistics concerning incidence of the disease and its complications in the various regiments. He considers the distribution and time of occurrence of the cases, the relation of dust and weather to the spread of infection, the incidence among colored organization, and concludes that (1) the incidence of the disease increases with the density of population in barracks. (2) That the hanging of a sheet between the individual beds in the barracks was of value in preventing infection. (3) That the negro race suffered much less from the disease than did the white. (4) That there were more cases complicated with pneumonia among the colored troops and that the disease was more fatal among them.

The Clinical Pathology of Mustard Gas (Dichlorethylsulphide) Poisoning, by GEORGE R. HERRMANN, M. S., M.D., Ann Arbor, Michigan.—(*Jour. Lab. and Clin. Med.*, November, 1918, No. 2, iv, 1). This writer concludes: (1) that mild cases of mustard gas burns of the

skin show no changes in the blood or urine. (2) Moderately severe and severe cases of mustard gas burns of the skin with some involvement of the upper respiratory tract show after the first week definite changes in urine, blood urea and blood. (3) The urinary changes consist in a diminution of the urinary output, increased concentration and acidity, albuminuria, and diminished urea and chloride output. In the sediment there may be found casts, renal epithelium, red blood cells and an increased number of leukocytes. Under forced fluids prompt improvement occurs. (4) Coincident with these urinary changes the blood urea is found to be high, but approaches normal with the improvement in the urinary condition when fluids are forced. (5) The blood shows a slight secondary anemia with a well-marked polymorphonuclear leukocytosis, a definite eosinophilia, and the appearance of myelocytes and young forms of leukocytes. The blood platelets were usually increased. No evidence of hemolysis was found. These changes indicate a disturbance in the white cell formation rather than in the red blood cell group. No leukopenia was noted at any time. The leukocytosis reached its height coincidently with the height of the secondary infection and fell with the improvement of the infection. (6) The temperature, pulse and respiration charts show in the severe cases an initial period of shock. With the development of the necrosis and the secondary infection there is a corresponding febrile reaction. (7) The bacteriological examination of the infected skin lesions and furuncles showed constantly the presence of Staphylococcus pyogenes aureus. In the one bronchial cast obtained streptococci were present. (8) We believe that the changes in the blood and urine may be interpreted as dependent upon the secondary infection and, in part, possibly, to the absorption of toxic products from the necrotic skin, rather than to any direct toxic action of mustard gas.

THERAPEUTICS

UNDER THE CHARGE OF

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An Experimental Investigation of the Cause of Early Death from Arsphenamine and of Certain Other Features of the Pharmacological Action of the Substance.—In the present series of experiments, JACKSON and SMITH (*Jour. Pharm. and Exp. Therap.*, 1918, xii, 221) have investigated the mechanism of acute death following the administration of arsphenamine. They studied especially the effects of various preparations of arsphenamine on the cardiovascular system with a view of discovering the cause of the acute reaction often seen in the clinic. They report that the slow injection of therapeutic quantities of arsphenamine in very dilute alkaline solution produces no striking results in anesthetized dogs. However, as the rate of injection and the concen-

tration of the drug are increased, toxic symptoms soon become manifest. The earliest of these symptoms consist in a dilatation of the heart, perhaps mainly of the right side at first; a progressively increasing pulmonary blood-pressure, and a slow, gradual, but not severe, fall of systemic pressure. The cause of the rise in pulmonary arterial pressure is believed to be due partly to the alkalinity of the solutions of arsphenamine used, and partly to the specific action of the drug itself. While the authors have not been able to prove that the formation of emboli in the pulmonary vessels may not be in part responsible for the increased pulmonary pressure, they believe that no such action as this occurs. With large, toxic doses, the right heart may have to contract against a pulmonary pressure increased by 100 per cent. above the normal, while at the same time the left ventricle may be contracting against a systemic pressure reduced by 25 to 50 per cent. below normal. These peculiar conditions may tend to establish a state of increased irritability and instability in the heart, and in rare instances may lead to delirium cordis. Drugs of the epinephrin type tend to increase the instability of the heart under these conditions. The reactions of the internal organs when arsphenamine is injected are variable. Apparently both central and peripheral influences are concerned. As a rule, oncometric tracings of the spleen and intestinal loop show a dilatation, while the kidney usually contracts, sometimes most vigorously. The toxicity of arsphenamine is not increased by the breathing of high concentrations of carbon dioxide nor by the injection of calcium hydroxide, calcium lactate or of monosodium phosphate. A number of intermediate compounds, occurring during the process of manufacture of arsphenamine, were also studied. None of these is very poisonous and none can account for the variable toxicity of the different samples of arsphenamine, which may or may not contain traces of one or more than one of these. The authors suggest that in those cases in which severe, acute, toxic symptoms suddenly manifest themselves, either during or shortly after the intravenous injection of arsphenamine, tyramine is more likely to be of benefit to the patient than is any other drug with which they are acquainted.

The Application of a Concentrated Solution of Magnesium Sulphate to Scalds and Burns.—MELTZER (*Jour. Pharm. and Exp. Therap.*, 1918, xii, 211) reports that burns of the first and second degree are invariably arrested in their development when molecular solutions of magnesium sulphate have been applied early. Third degree burns run, as a rule, a more favorable course under the application of magnesium sulphate than under any other treatment. Higher concentrations than 25 per cent. seem to exert a still better influence. The favorable action of the application of magnesium sulphate in advanced stages of burns of the second and third degree is less striking, especially on account of the infection present, but even then it seems to exert a favorable influence and ought to be used in combination or alternatingly with antiseptics.

GYNECOLOGY

UNDER THE CHARGE OF

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Magnesium Sulphate Solutions in the Treatment of Spastic Contractures of the Rectum and Sigmoid Colon.—Through repeated sigmoidoscopic and roentgenologic studies, SOPER (*Am. Jour. Med. Sc.*, 1918, clvi, 205) has found that spastic contractures of the lower colon and rectum of varying intensity play an important part in the etiology of many cases of chronic constipation and of the gas pains and abdominal distention following operations on the abdomen and pelvis. The most frequent site for these contractures is the rectosigmoid juncture, severe contractures at this point presenting a syndrome described by the writer as "sigmoido-spasm." A most obstinate form of constipation, he finds results from combined contractures and dilatations, *e. g.*, (*a*) atony of the rectum and sigmoid associated with contracture at descending colon; (*b*) contraction at the rectosigmoid angle and atony of the sigmoid loop; (*c*) contracture at the splenic flexure and descending colon and atony of the cecum. The contractures, he feels, are the result of disturbances in Meltzer's law of contrary innervation, a predominance of stimulation occurring in the exciting or contractile phase. Reasoning on the basis of Meltzer's experimental work, which showed that solutions of magnesium sulphate produce an inhibitory influence upon peristaltic movements of the intestinal tract when the salt is given intravenously or applied directly to the mucosa, the writer has applied a saturated solution of magnesium sulphate directly to the contractures in a series of 220 cases. He applied the solution by means of cotton applicators through the sigmoidoscopic tube (knee-chest position), a diffuse, pink color appearing in the mucosa within from ten to twenty seconds. Mild contractures disappeared in a few seconds. Moderate contractures required a minute or two, and in order to relax strong spasms a series of applications were necessary. Of 80 cases of obstinate constipation, 68 cases were apparently completely restored to a condition of normal colonic function. The number of treatments required in these cases varied from ten to thirty applications given every second or third day. Five cases were complicated by inflammatory induration and distortion of the bowel at the rectosigmoid junction, consequently treatment was ineffectual. In 7 cases the contractures were overcome, but normal colonic function was not restored. Of 72 cases of obstinate spastic constipation, *i. e.*, cases that were of long standing but that had not been previously under his care, 64 were successfully treated, with satisfactory restoration of bowel function. Eight cases were extremely neurotic individuals who could not stand the treatment, although no real pain is produced by it. Sixty-eight cases of obstinate spastic constipation, cases of long-standing constipation, but which presented contractures that were moderate in character, *i. e.*, that readily responded to treatment and required but from six

to ten applications to restore good colonic function. The patient is asked to return for treatment every second day, the interval between treatments being gradually lengthened. All purgatives and water enemata are discontinued; an oil enema may be used if the patient is unable to come for treatment at the proper time. If the contracture cannot be reached through the sigmoidoscope, two ounces of the solution may be injected by passing a soft-rubber catheter through the sigmoid tube. Roentgenological examination in a series of 6 cases of postoperative abdominal distention and gas pains showed that the colon alone was involved; sigmoidoscopic examination showed the presence of marked contractions in the rectum and lower sigmoid. In a series of 30 such cases an enema of saturated solution of magnesium sulphate was given according to the following technic: Three ounces of saturated solution of magnesium sulphate is introduced by means of the rectal tube passed four or five inches into the bowel, elevating the hips whenever possible and having it retained as long as possible. This procedure may be repeated every day or several times a day if so desired. There was immediate relief in 24 cases. While the enema was usually retained only about five minutes, there were no toxic effects when it was retained for twenty-four hours.

Rational Preoperative Treatment, with Special Reference to Purgation.—In a recent paper PEET (*Jour. Am. Med. Assn.*, 1918, lxxi, 175) has pointed out the many advantages of the simple enema over the various forms of pre-operative catharsis so widely employed. The administration of cathartics on the night preceding operation is followed almost invariably by loss of sleep, psychic and physical weakness, loss of body and intestinal fluids, change in the bacterial flora of the intestine, hypotonicity of the intestinal wall and irritability of the rectum and lower colon. Postoperative thirst after such a preparation must necessarily be greater, and because of the higher degree of irritability of the rectum, thirst cannot be relieved by the easiest and safest method. It is impossible, even with a powerful purgative, to eliminate all the intestinal products which might lead to putrefaction, since waste products are continuously passing into the intestines. Moreover, attempts at sterilization by calomel and other drugs, the writer feels, are useless. While many organisms are carried out, there is a tendency to change in the bacterial flora, usually in the direction of multiplication of fermentative organisms. Clinical evidence favors a change to the simple enema. For the past six years a careful study was made of patients receiving pre-operative catharsis and those receiving the simple enema only. In the latter cases postoperative thirst, nausea and vomiting occurred much less frequently, and the patients were in much better mental and physical condition at the time of the operation.

Is the Purgation of Patients Before Operation Justifiable?—On the basis of an extensive clinical and experimental study, ALVAREZ (*Surg. Gynec. and Obst.*, 1918, xxvi, 651) goes a step further than the previous article and advocates that even the simple pre-operative enema be avoided unless absolutely necessary, that food be given as late as possible before operation, that water and solid food be given by mouth as soon after operation as possible and that purgatives should be abso-

lutely avoided both before and after operation. The writer sums up his reasons for avoiding purgatives before operations as follows: (1) Some of the purgatives owe their effects to the fact that they are irritant poisons that must be removed quickly from the body. Others act by interfering with intestinal absorption and by upsetting the balance of salts. In either case they bring about pathological conditions. The body is weakened and not strengthened. (2) We know now that the dehydration of the body and the upset in salt balance are bad, particularly before an operation in which there may be hemorrhage and vomiting. (3) With magnesium sulphate there may be an increased amount of fluid in the bowel to disturb those who want it empty. In operations on the colon, liquid contents are more difficult to control mechanically than are solid masses. (4) There is an increased growth of bacteria. There is some evidence that there is an increased absorption of toxins, and a greater permeability of the mucous membrane to bacteria. Undigested food may be carried down into the colon to supply increased pabulum for the bacteria. (5) By weakening some parts of the bowel and making others more irritable the even flow of material from stomach to anus is rendered impossible. (6) Whether from disturbances in motility, in absorption, in the circulation or in the bacterial conditions there certainly is a tendency to flatulence and distention. (7) When the bowels must move frequently during the night the loss of sleep is considerable. The purgation is particularly trying if the patient is wearing a large cast, has a broken leg or other painful lesion which makes each resort to the bedpan an ordeal. (8) If the patient should happen to have some intestinal obstruction, a gangrenous appendix, a badly diseased Meckel's diverticulum or adhesions forming around some pus, purgation may directly cause death. (9) Purgation makes the bowel react so poorly to drugs that there may be grave difficulties in meeting postoperative emergencies. (10) Emptying the bowel by starvation and purging makes the resumption of colonic activity much more difficult. The colon must be filled and distended to a certain extent before it will empty. (11) The fact that children and nervous women will sometimes begin vomiting during the night, before the operation, shows that the purge must be responsible for some of the postoperative nausea and vomiting. The ether adds the finishing touches to what was begun the night before. These conclusions were reached as the result of a series of experiments on purged animals conducted by the writer and F. B. Taylor. They studied the effects of castor oil, magnesium sulphate, cascara, calomel and tincture of jalap on rabbits by excising segments of the intestines from five different points, placing them in warm oxygenated Ringer's solution and noting changes in the gradients of rythmicity, irritability or latent period. Only mildly laxative doses were used; the drugs were given at noon and the animals killed next morning. The bowels were found injected, full of fluid and gas, sometimes atonic and flabby, often irritable here and there and inclined to contract down into hard white cords. When the segments were placed in Ringer's solution their contractions were weak and irregular and they soon became fatigued. One of the most important points noted was the diminished sensitivity to the local application of drugs, some having to be increased one hundred times. Magnesium sulphate appeared to be the most objectionable from the surgical standpoint,

since by preventing the absorption of water it causes great distention of the bowels with fluid. Calomel and cascara did not cause such pronounced signs of poisoning and fatigue in the excised segments as did castor oil, magnesium sulphate and jalap. The segments from the calomel rabbits beat well with a large amplitude and slow regular rhythm. The gradient of rhythm showed irregularity only in the animals that had received castor oil. The latent periods of the segments showed marked deviations. Some segments showed an abnormally high degree of irritability with a very short latent period, others scarcely respond to the strongest current. Normally the latent periods are graded from short ones in the duodenum to longer ones in the ileum. The engorgement of the mesenteric vessels and the injection of the intestinal wall were quite sufficient to upset the delicate balance between the gases in the intestine and those in the blood. Besides omitting the purgative the night before, the writer suggests that if the operation is not to be performed earlier than 10 A.M., a light breakfast may be eaten, although in occasional cases, of course, fear and apprehension may lengthen the emptying time of the stomach. Enemata should be given only to those who are definitely constipated or who are to have an operation on the lower colon or on the pelvic organs. Furthermore, gas-oxygen should have preference over ether whenever possible, as its effects on the digestive tract are much less. The importance of giving solid food as soon as possible after operation is strongly emphasized by the writer, because of its tonic effect on the tract, but cellulose should be avoided. The postoperative use of purgatives is quite as bad as their pre-operative administrations.

Vertigo of the Menopause.—Although vertigo is seldom the only prominent symptom of the menopause, since it is almost always accompanied by such disturbances as hot and cold flashes, cold perspiration, palpitation, blurred vision, flickering before the eyes, headache, nausea, etc., nevertheless it is one of the most interesting phenomena that occur at this important time of life and has been the subject of investigation by SANES (*Am. Jour. Obst.*, 1919, lxxix, 7). Like most other investigators who have studied this condition, he attributes the vertigo to a lack of the internal secretion of the ovary and most of his contribution has to deal with the question of treatment. Before any plan of treatment is decided upon, one must make sure that the case is one of climacteric vertigo. Such pathological conditions as lesions of the internal ear or of any other part of the balance mechanism, such diseases as cardiovascular, renal and ocular, especially muscular unbalance of eyes, must be excluded. If the case can be definitely diagnosticated as that of climacteric vertigo, the treatment must always be that of the menopause in general, As the metabolism is almost always below par in the menopause, the nutrition and elimination of the patient must be looked after and, as the insufficiency or absence of the ovarian internal secretion is the underlying cause of the symptoms, ovarian organotherapy is logically indicated. Sanes reminds us however, that we do not know the active principle of the internal ovarian secretions; in fact, we do not even know definitely which part or parts of the ovarian substance (Graafian follicle, corpus luteum or the interstitial cells) is responsible for the internal secretion. It seems plausible there-

fore, that if by the administration of glandular tissues we can successfully replace a deficiency in internal secretion of the gland, the whole ovarian substance, in the present state of organotherapy, should meet best the needs of a menopause patient. For this reason Sanes prefers using the whole ovarian substance in the treatment of climacteric disturbances in general and vertigo in particular. There is one difficulty that is met by those who prescribe glandular extracts and that is the lack of standardization of the preparations. One must specify the name of the manufacturer or the proprietary name of the ovarian preparations to get the dosage desired, since one manufacturer will base the dosage of an ovarian preparation on the quantity of the *fresh* ovarian substance in it, while other manufacturers will base their product on the amount of *desiccated* substance contained. Sanes uses a preparation of ovarian extract, each grain of which represents a grain of the fresh ovarian substance, the dosage being 5 grains two to four times a day. Larger doses were only occasionally found to be of any more benefit than the small doses routinely used. In this study, the records showed that about 37 per cent. of the cases were improved, while in 25 per cent. there was complete control of the vertigo by using the ovarian extract. In an occasional case, the addition of a small dose of thyroid extract to the ovarian extract seemed to have been a benefit.

Pathology of Chronic Metritis.—Chronic metritis and chronic subinvolution of the uterus are two gynecological conditions, which, until recently, have been considerably confused and although these terms are frequently used by practitioners, they are frequently used interchangeably and many times when the user has a hazy conception of the condition that he is describing. It might be worth while then, to glance at the conclusions reached by SCHWARZ (*Am. Jour. Obst.*, 1919, lxxix, 63) in a rather extensive study of this subject. He states that chronic subinvolution alone is by far the most frequent cause of enlarged uteri, causing hemorrhage, pain or leucorrhea. The thickness of the uterine wall is due, in order of their importance, to an increase of the elastic tissue, edema and liquefaction of the connective tissue and hypertrophy or enlargement of the individual cells. Chronic metritis as a true inflammatory condition does exist and is frequently responsible for the symptoms in these enlarged uteri. However, chronic metritis locally is never a primary disease, but is secondary to chronic endometritis, chronic salpingitis or chronic inflammation within the pelvis. It should be remembered that chronic subinvolution and chronic metritis may coëxist in the same uterus. Chronic pelvic inflammation is only occasionally seen in connection with chronic subinvolution and therefore other factors must play a greater role in the production of this condition; for example, in Schwarz's series of 38 cases, there were only 6 that showed inflamed appendages and only 7 had chronic endometritis. Schwarz believes that the term "chronic metritis" should be abolished from the clinical standpoint. The term chronic subinvolution might be substituted in cases of multiparous uteri, which are definitely enlarged, and cause symptoms without evidence of pelvic inflammation. This would probably include over 80 per cent. of the uteri which, pathologically show signs of chronic subinvolution. The term chronic metritis might be applied to those cases in which there

is evidence of pelvic inflammation in connection with a more or less immovable uterus. This would, in all probability, embrace a greater portion of cases of true chronic metritis, as well as those in which there is a distinct overlapping of both conditions. In addition to placing a majority of these cases, clinically, in a class descriptive of their pathology, there is another advantage of using the term chronic subinvolution, since the frequency of its occurrence will be constantly impressed upon the observer. The condition, of necessity, must result from a lack of involution of the puerperal uterus, therefore its prevention lies in the proper care of patients during pregnancy labor, and the puerperium.

OPHTHALMOLOGY

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Ocular Affections in Typhoid.—DANTRELLE (*Inaugural Thesis, Annali, D'Oculist*, October–November, 1918, p. 529) has studied ocular manifestations observed during an epidemic of typhoid fever. He classifies them as symptoms and complications. *Symptoms:* Conjunctival hyperemia occurs ordinarily with the rise in temperature, frequently intense, it continues at times during the entire febrile period and occasionally even during defervescence. The frequency of this symptom is shown by the fact that during an epidemic many cases are sent to the ophthalmic departments with the diagnosis of acute conjunctivitis when the case is one of typhoid fever. Subconjunctival ecchymoses of the size of a head of a pin to that of a pea are frequently observed upon the course of a subconjunctival vessel, and occupying the inferior cul-de-sac or the bulbar conjunctiva near the limbus. Ciliary alopecia is inconstant; it sometimes accompanies alopecia of the hairy scalp. Myosis occurs as does also photophobia. The fundus frequently presents slight hyperemia of the papilla which recovers entirely. *Complications:* Complications are observed in about 1 per cent. of the cases; Dantrelle has noted 65. He divides them into those due probably to the unknown organism of the disease; these are quite rare, the others occur during convalescence and are caused by adventitious infections. Cataract (7 cases) begins on the tenth to the fifteenth day of the disease; it is accompanied by discoloration of the iris; as the subjects are usually young, the cataract is soft. Alterations of the fundus (11 cases) consist either in papillary lesions or in those of the retinal circulation. These lesions are characterized by a vascular pigmentation; the pigment surrounds the arterial or venous branches forming a pigmented network upon the vessels; they are accompanied

by grave and definite functional disturbances. The papillary lesions are simple atrophy following optic neuritis. Ocular palsies (3 cases) of the third or sixth pair have occurred during the height of the affection. As complications of convalescence, the author notes palpebral abscess, orbital phlegmon, corneal ulcers, optic atrophy following erysipelas, or phlegmon of the orbit. These late complications are due to the streptococcus; antistreptococcic serotherapy appears to be of some service.

Acute Anterior Ethmoiditis in Young Subjects.—STEPHENSON (*British Jour. Ophthal.*, No. 8, ii, 416) writes that in his experience a form of unilateral orbital inflammation or suppuration is not infrequent in young children under five years of age, although its essential nature is not always recognized. Many of the milder cases recover spontaneously with or without a discharge of pus from the nostrils or into the nasopharynx. A certain number of cases are diagnosed at a later stage as orbital cellulitis, as shown by tenderness, edema and redness of the eyelids, chemosis and protrusion and impaired motility of the eyeball, which is usually displaced downward or downward and outward. General symptoms, such as fever, headache, vomiting, etc., are usually present in the more severe cases. As a rule, there is no history of injury, or of erysipelas, or any other local or general malady or illness. The reporter believes that this group of cases can be best explained by an acute inflammation of the anterior ethmoidal cells: in certain of the more severe cases the posterior ethmoidal cells may also be involved. The condition is not accompanied by any ophthalmoscopic nor rhinoscopic signs. Recovery is the rule under the simplest measures. When symptoms are severe, or the general condition of the patient is threatening, surgical measures must be adopted: an incision into the orbit over any spot which seems to indicate underlying pus. If nothing escapes, the dressing forceps, with closed blades, are introduced into the depth of the wound, and the blades of the instrument are then more or less widely separated; pus may make its appearance two or three days later. The writer has adapted as a routine measure a somewhat different procedure, which consists of raising the bone over the region of the anterior ethmoidal cells when pus usually escapes. The prognosis is favorable.

Blood Cysts of the Orbit.—GIFFORD (*Am. Jour. Ophthal.*, September, 1918, p. 625) concludes that in every case of deep-seated orbital tumor of uncertain nature the possibility of blood cyst and some other benign cyst should be considered. If an operation is done the tumor, on being exposed, should be secured by passing a thread through it and its nature tested by puncture. If it proves to be a cyst, thorough cauterization with phenol or something similar should be tried before an attempt is made to extirpate it.

Observation of the Fundus During Temporary Blindness.—ORMOND (*British Jour. Ophthal.*, May, 1918, p. 273), during an attack of ephemeral amblyopia, observed in the fundus four or five distinct notchings of the inferior retinal vein, which suddenly disappeared, with simultaneous return of the vision; the pupil, which was enlarged during the

crisis, became contracted. The reporter thinks the condition to have been due to contraction of a central artery entailing pallor of the disk and surrounding retina, with a diminution of blood in the vein, causing the endothelium of the vein to become wrinkled into horizontal folds as the vessel became empty. Neither cardiac, vascular nor renal disease was demonstrated.

Tuberculin in Ocular Disease.—VERHEYDEN (*British Jour. Ophthal.*, April, 1918, p. 223) finds that tuberculin gives good results in phlyctenular kerato-conjunctivitis, especially as regards photophobia, blepharospasm, lacrimation, but does not prevent relapses, although the latter when they occur are milder; the usual local treatment is also employed. Scleritis and episcleritis are more rebellious; the other etiologic factors of these affections should be eliminated before having recourse to tuberculin. One case of iridocyclitis, probably bacillary, recovered by local treatment and six injections of tuberculin. One case of paralysis of the third pair, of tubercular origin, with double ptosis, paralysis of the right superior rectus and slight diplopia, recovered after a relapse during the course of the treatment, which consisted of six injections of tuberculin (0.001 to 0.009) made during an interval of nine months.

A New Sign of Death.—LECHA-MARZO (*Archiv Med. Belg.*, March, 1918, p. 271) calls attention to a sign of death applicable in civil life as well as upon the battle-field. It consists in placing a piece of turmeric paper upon the globe under the lids; in life, slight pressure gives a bluish spot, but no change in color is observed in the cadaver; in fact, the red color at times appears more pronounced. In the living, ocular acidity is never observed; immediately after death the reaction is slightly alkaline as in life, shortly after death the reaction is neutral and finally acid. This ocular acidity makes its appearance almost uniformly during the eight hours following death.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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Method of Collecting Blood for the Wassermann Test.—WANG (*Jour. Path. and Bact.*, 1918, xxii, 85) advocates a simple method for collecting the patient's blood for the Wassermann reaction. The blood is collected upon pieces of filter paper about the size of a dime. This blood can easily be obtained as a drop from the finger or the lobe of the ear. He estimates that each drop collected in this way upon the paper contains 0.04 c.c. of serum. Upon collection, these small pieces of paper

are allowed to dry and then are used in the regular system for carrying out the Wassermann reaction. Each paper represents a unit of patient's serum. In place of the measured fluid serum the slip of paper is added to the series of tubes. He claims that the results are very satisfactory and it is quite easy to standardize the individual systems to give satisfactory results with this mode of collection. He points out that this method has great convenience for obtaining blood in private houses when other facilities are not at hand.

Agglutination Reaction of the Meningococcus Against Carriers.—Since the beginning of the War in 1914 much importance has been laid upon meningococcus carriers. The determination and segregation of individuals having pathogenic meningococci within the nose became of great importance for the prevention of meningitis among the soldiers. Various methods have been advocated for the determination of the meningococci. During the first two years, the recognition of this organism from other Gram-negative cocci was carried out by cultural tests upon carbohydrates (dextrose, levulose and saccharose). VINES (*Jour. Path. and Bact.*, 1918, xxii, 56) compares the results of the analyses of the first two years with those of the third year when the determination of the Gram-negative organisms was carried out by serological tests. By this means organisms which are morphologically similar were divided into four groups. His analyses showed that the number of carrier cases among the troops has increased, while the number of cases of meningitis also became greater. It was also demonstrated that various types of Gram-negative cocci may be present in the nasal secretion at the same time. Some of these types can be separated by the fermentation reaction while others are recognized only by the serological test. It was found, moreover, that certain cases periodically showed the presence of meningococci with intermissions of negative cultures. In these it is suggested that the source of infection may lie in the sphenoidal sinus which periodically discharges them. The author believes that certain spontaneous variations may occur in the agglutination reaction of the meningococci in the nasopharynx.

Encephalitis Lethargica.—For several months past reports have appeared in England and upon the continent of cases of botulism, hemorrhagic poliomyelitis and encephalitis. Gradually it was recognized that these various reports were referring to a common condition which is being discussed under the heading of encephalitis lethargica. MOTT (*British Med. Jour.*, 1918, ii, 488) discusses the cerebral lesions. Punctiform hemorrhages were found in the neighborhood of the floor of the fourth ventricle, the third ventricle and in the pons. The cerebral cortex also showed some reaction associated particularly with small hemorrhagic lesions of the meninges. The minuter characteristics of the lesion indicate that there is a non-suppurative inflammation particularly surrounding the bloodvessels and to some degree resembling the reaction observed in poliomyelitis. Degenerative changes are also present in the nerve and glial cells. The disease has assumed epidemic prevalence in some localities in England. The causative agent is not known but it is interesting that a similar disease has previously been described following epidemics of influenza.

The Biochemistry of Bacillus Histolyticus.—In a previous paper WOLF and HARRIS investigated the problem of carbohydrate metabolism of B. welchii and B. sporogenes. In those investigations it was shown that the B. sporogenes was unusually active in decomposing proteins to amino acids and ammonia. Both organisms produced butyric acids and small quantities of acetic acid. These authors continued their studies upon the metabolism of anaërobic bacteria and now report the results obtained with B. histolyticus (*Jour. Path. and Bact.*, 1918, xxii, 1). This organism appears to be the most active destructive agent in anaërobic infections. It may be associated with other types of anaërobes which assist the activity of the B. histolyticus. In tissues the organism appears to melt down the muscle and soft structures denuding the bone in a process of liquefaction. These studies were undertaken upon cultures in various media. It was shown that it is essentially a protein-splitting organism attacking certain proteins with great intensity. Amino acids and ammonia are formed in the reaction along with large quantities of butyric and acetic acids. During the growth of the organism in rich protein media considerable quantities of crystalline tyrosin are formed.

Multiple Skin Metastases from Cancer of Internal Organs.—SUZUKI (*Jour. Cancer Res.*, 1918, iii, 357) has collected 110 cases from the literature and 5 of his own wherein metastases have arisen in the skin from internal cancers. Skin metastases are quite unusual in all forms of cancer and it is interesting that there are certain types which are prone to induce such localizations more commonly than others. In the majority of instances the primary tumor was in the stomach, intestine or uterus. They appeared slightly more commonly in the female than in the male. Curiously enough in 11 such cases reported from Japan the frequency of male to female is reversed in the proportion of 9 to 2. This the author believes is because cancer in general is more common in the male than in the female in Japan. These skin metastases are usually of the nature of adenocarcinoma and make their appearance upon the thorax and abdomen in the majority of cases. Next in frequency are the back and neck. It is not clear why this disposition upon the skin surfaces should take place. In certain regions the localization of the metastases in the skin is dependent upon a rich and neighboring lymphatic supply. The presence of skin metastases is of serious prognosis, the majority dying within three months.

Occupational Cancer.—For a number of years evidence has been accumulating to indicate the importance of certain factors in occupations causing a predisposition or as some would have it, producing a precancerous state whereby malignant tissue changes more readily arise. For the most part we have been willing to accept the fact that certain types of damage have a greater tendency to bring about these particular predisposing changes than others, and there is little information other than studies upon morphological changes, suggesting the underlying factors which relate these new tissue states to the development of neoplasm. H. C. Ross (*Jour. Cancer Res.*, 1918, iii, 321) has collected the evidence in Great Britain of the occupational factors associated with new growth. He has particularly interested himself

in coal, coal-tar and its derivatives. He finds that the derivatives of different kinds of coal differ somewhat in their qualities of inducing the precancerous conditions and he finds also that the pitch of gas works is much more harmful than that obtained from the blast furnace. He points out that the factor of mechanical irritation as induced by coal is much less important than the chemical stimulus of coal derivatives. Thus he finds that the various partially refined products contain a quality which is not as evident in the original coal nor in some of the highly refined products of different chemical constitution. In this way he compares the effects of coal, tar, pitch, soot, anilin dyes and petroleum. He compares these results with those obtained in kangri bruns, tobacco, bettle-nut, *x*-ray ulcers, etc. After reviewing the importance of these various types of semi-experimental cancer he applies his theory of auxetics advanced in 1911. The author believes that these stimulating substances or auxetics are produced in decaying organic matter and are either of endogenous or exogenous origin. Thus in chronic ulcers the decomposition of the individual's own tissues gives rise to these unknown chemical stimuli, while similar or allied bodies arise in manure and the slow decomposition of organic matter as seen in the coal deposits. With this theory based upon the properties of such indefinite and unknown substances there is much opportunity for speculation with little definite information, however, for advancing an understanding of the cancerous process.

A Case of Mucor Infection.—It is quite unusual to find any of the types of mucor pathogenic to man. ERNST (*Jour. Med. Res.*, 1918, xxix, 143) reports the isolation of a M. corymbifer from a healthy young adult who was suspected of suffering from tuberculosis. Clinically no lesion could be demonstrated in the chest but there were a number of ulcers upon the vocal cords. The examination of the sputum was repeatedly negative for tubercle bacilli, but on several occasions the mucor was demonstrated in the stained smears and was also isolated in culture. It is suggested that the infection may have been gained from working with cereal products where this type of mould is not uncommon.

Studies on Uranium Poisoning.—KARSNER and his associates (*Jour. Med. Res.*, 1918, xxix, 157) undertook a study of the poisonous effects of various uranium salts. They point out that although uranium is one of the less frequent metals met with, yet with the development of certain war industries it was being used as a substitute for tungsten in the making of alloys. Under these conditions it is possible that fair quantities of uranium may find their way in the shape of powder and dust into the respiratory and digestive tracts. It is mainly in the form of the uranium oxide that this contamination may occur. The uranium oxide in itself is insoluble in water and as such can be non-toxic. But these authors have shown that because of its solubility in hydrochloric acid the presence of uranium oxide in the stomach may lead to a sufficient solution and absorption to cause intoxication. Such was actually demonstrated in the experiment. The various salts of uranium all show poisonous effects, the action being mainly upon the kidney. The authors were able to show that the main excretion is accomplished by

way of the kidney and that the severity of the functional and anatomical disturbance is due to the concentration of the metal in this organ. The presence of uranium in the kidney is not because of a special affinity of the kidney tissue for uranium but rather the accumulation of it through the functional activity of excretion. The authors were also able to demonstrate by an experiment that a state of acute intoxication was largely one of an acid intoxication following upon the kidney lesion. They indicate that the amount of acid intoxication is in proportion to the kidney lesion and that the kidney disturbance precedes the evidence of decreased alkali reserve in the blood.

Brom Cresyl Purple and Litmus as Indicators for the Classification of Tubercle Bacilli.—It is desired in bacteriology to devise a technic which will indicate the biological activity of microörganisms during the period when they are under observation. Not a few cultural methods are in practice for this purpose. Many tests are used for demonstration of the production of acid by particular organisms from various materials. The usual methods in use do not indicate quantitatively the production of these acids. The H-ion concentration can, of course, be determined in the cultural media at any particular period but the method becomes cumbersome if it is to be applied repeatedly to the same culture or to many different observations during a given study. It is to be found that there are certain indicators which by a color reaction give a fairly wide range of color display in different reactions of the medium. Some of these indicators differentiate both the grades of alkalinity as well as acidity. With this in mind FROTHINGHAM (*Jour. Med. Res.*, 1918, xxix, 153) has studied the variation in the color display of two indicators with particular reference to the reactions taking place in cultures of tubercle bacilli. Theobald Smith has by titration methods shown that the human strain of tubercle bacilli when growing in a glycerine broth tends to cause a primary alkaline reaction followed by an acid production, while the bovine type produces a primary alkalinity which is not followed by acid production although the amount of alkalinity after weeks of time is somewhat diminished. The presence of brom cresyl purple in the culture demonstrated fairly well the development of alkalinity by a purple color and a light lemon-yellow color when acid appeared. All gradations between these two colors lay between the distant extremes. With the use of litmus a somewhat similar but less satisfactory result was obtained. The author points out that by a careful study of such color reagents and with a definite knowledge of the meaning in terms of the H-ion concentration of definite shades of color much use may be obtained by the application of these indicators.

A Study of Experimental Organizing Pneumonia.—Recent years have demonstrated that there is much still to be learned respecting pneumonia. This is true not only of its epidemiology, bacteriology, but also of its pathology. We are realizing more than formerly that the types of inflammatory reactions within the lung are dependent upon definite factors which may be determined and that the vagaries so often noted are not merely the chance development of peculiar reactions. Best known to us is the sequence of events in lobar pneumonia of pneumococcus origin. When, however, any differences occur from the usual

train of pathological events we are still largely at sea in appreciating fully what has taken place. One of these unusual events is the occasional organization taking the place of the more common complete resolution. For some reason the lung parenchyma responds to an irritant in a manner not unusually observed in pneumococcus pneumonia. WADSWORTH (*Jour. Med. Res.*, 1918, xxix, 147) undertook an experimental research attempting to reproduce the condition found in the human. He made use of dogs, using the Meltzer method for the production of pneumonia. A number of animals were infected with the pneumococcus. None of these showed evidence of organization. Another series of animals was infected with the Staphylococcus aureus. These animals developed bronchopneumonic lesions in which resolution was delayed and the beginning of abscess formation observed. The third series of animals received a mixture of pneumococcus and staphylococcus. By these means it was hoped to obtain more extensive lobar lesions by the pneumococcus which might favor the activity of the staphylococcus with delayed resolution and organization. Difficulty was experienced in gauging the proper dosage and many of the experiments were negative. Two animals, however, killed on the fifteenth and nineteenth day, showed irregular areas of consolidation around the bronchi, partly acute and partly unresolved with early organization. The experiments indicate that the pneumococcus will give rise to unresolved pneumonia with organization only in the presence of a complicating or secondary infection. It is possible that with certain organisms constituting the secondary infection a symbiosis with the pneumococcus is necessary to permit them inducing the proper grade of reaction whereby organization results. It is of course also to be remembered that there may be other bacteria acting in pure culture which may produce types of organizing pneumonia, as has been suggested by MacCallum and Cole, as for instance the pulmonary streptococcus infection following measles.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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Safe Limit of Carbon Dioxide in the Working Atmosphere.—HIGLEY (*Am. Jour. Public Health*, July, 1918) states that in the opinion of Flügge one may breathe for several hours air containing twenty times the usual permissible percentage of carbon dioxide without perceptible deleterious influence upon his health. The more rigorous methods of the New York State Commission for Ventilation reveal

the fact that stagnant air containing two to fifteen times the generally accepted amount of carbon dioxide may be respired seven hours per day for five or more weeks with no perceptible effect upon heart-rate, on increase of heart-rate on standing, on blood-pressure, Crampton value or respiration of the subject. On the other hand, all the deleterious effects that were formerly attributed to respiring carbon dioxide present in the stagnant air may be produced by breathing, for the same period, air that is practically free from carbon dioxide but which has a temperature of say 90° F. and a very high relative humidity. Also that a cold, dry air when heated to 80° or more without humidification may produce, when respired for some time, the deleterious results so beautifully demonstrated by Cocks. The matter is well summed up by Professor Lee when he says that "the problem of ventilation is physical rather than chemical, cutaneous rather than respiratory." In view of the fact that recent investigations have apparently shown carbon dioxide to be harmless when respired in much larger amounts than 0.08 per cent., the writer suggests that the safe limit of this gas in the working atmosphere be placed at 0.2 per cent.

Sterilization of Woollen Blankets and Uniforms.—FULTON and STANIFORD (*Jour. Am. Med. Assn.*, September 7, 1918, p. 823) state that the following procedures effectively sterilize woollen goods without deterioration or shrinkage: Woollen blankets or uniforms are placed on hangers or loosely on the trays in the sterilizer. Sixty pounds of steam is introduced into the outer jacket of the sterilizer to prevent subsequent condensation of steam within the sterilizing chamber. A vacuum of from fifteen to twenty inches is created in the sterilizer chamber to facilitate penetration of the clothing by steam. Sterilization is performed with either 0 pounds of steam for one hour, designated as the atmospheric pressure method, or 12 pounds of steam for ten minutes, designated as the pressure method. Again a vacuum of from fifteen to twenty inches is produced to facilitate drying. The door of the sterilizer is opened about four inches for ten minutes to allow gradual cooling of the contents of the sterilizer.

Studies in Bovine Mastitis. II. The Relation of Hemolytic Streptococci to Udder Infections.—JONES (*Jour. Exper. Med.*, September 1, 1918) states that hemolytic streptococci produce more or less severe inflammations of the udders of cows. Frequently infected quarters are swollen, firm, hot and tender. In a number of instances it has not been possible to detect gross changes in the mammary gland. While invasion of the udder with hemolytic streptococci has not been observed so frequently as infections with non-hemolytic types, nevertheless serious losses occur from these infections. Of nineteen cows under observation for an extended period, only four recovered. The udder may become invaded at any time during the lactation period. Doubtless the principal method of entrance is through the teat canal. Injuries play only a minor part as a predisposing factor. Animals suffering from mastitis in one quarter associated with hemolytic streptococci frequently shed identical streptococci in the milk from other quarters. Often the organisms are in pure culture or make up the bulk of the flora of that quarter. These invasions rarely produce gross changes in the gland

and frequently fail to change the character of the milk. Cows affected in this way are of considerable danger to other animals in the herd. The milker is usually warned of the infectious nature of the secretions of the diseased quarter, but may be careless in handling milk from apparently normal quarters. This may explain one ready source of infection. The pathogenicity of hemolytic streptococci obtained from cases of mastitis to species other than bovines is undetermined. Raw milk from large dairies must contain a considerable number of these organisms. Usually only the milk from clinically affected quarters is discarded, but the secretion from the other quarters not visibly involved which often contains large numbers of streptococci enters the milk supply. If any considerable number of these organisms were pathogenic for consumers of milk, septic sore-throat would occur with considerable frequency; nevertheless, milk containing a few flocculi and hemolytic streptococci obtained from cows which fail to show gross lesions must be looked upon with suspicion until more is known of the source and nature of the virus.

Attempts to Induce Poliomyelitis in Small Laboratory Animals.—STIMSON (*Hygienic Laboratory Bulletin*, No. 111, p. 31) states that no evidence was adduced by his experiments to show that rabbits, guinea-pigs or rats are susceptible to poliomyelitis. Other observers have reported the successful infection of rabbits and guinea-pigs with poliomyelitis virus. Their methods did not differ essentially from those employed by Stimson. The discrepancy, therefore, must be attributed to one or the other of two causes, according to Stimson: either the strain or virus employed by these observers differs from his in its pathogenic properties or it is contaminated with some organism capable of producing these symptoms in small animals.

Epidemiological Studies of Poliomyelitis in New York City and the Northeastern United States During the Year 1916.—LAVINDER, FREEMAN and FROST (*Public Health Bulletin No.* 91, July, 1918) state that poliomyelitis is, in nature, exclusively a human infection, transmitted from person to person without the necessary intervention of a lower animal or insect host, the precise mechanism of transmission and avenues of infection being undetermined. The infection is far more prevalent than is apparent from the incidence of clinically recognized cases, since a large majority of persons infected become "carriers" without clinical manifestations. It is probable that during an epidemic such as that in New York City a very considerable proportion of the population become infected, adults as well as children. The most important agencies in disseminating the infection are the unrecognized carriers and perhaps mild abortive cases ordinarily escaping recognition. It is fairly certain that the frank, paralytic cases are a relatively minor factor in the spread of infection. An epidemic of one to three recognized cases per thousand, or even less, immunizes the general population to such an extent that the epidemic declines spontaneously, due to the exhaustion or thinning out of infectable material. Apparently an epidemic incidence relatively small in comparison to that prevailing in an epidemic may produce a population immunity sufficient to definitely limit the incidence rate in a subsequent epidemic. It is, of course,

to be expected that further experimental and epidemiological research will modify this view and will more fully explain all the phenomena of this disease. It may, however, be noted that other more common infectious diseases, generally considered "familiar," present problems as little explained as those of poliomyelitis and that broader studies of these diseases may be expected to assist in interpreting some of the facts established regarding poliomyelitis.

A Clinical Study of the Frequency of Lead, Turpentine and Benzine Poisoning in Four Hundred Painters.—HARRIS (*Arch. Int. Med.*, August, 1918, xxii, 129–156) undertook this study to obtain a more concise idea of the extent to which actively employed workers, most of whom thought themselves in excellent health, gave evidences of damage inflicted by lead paints. One hundred and sixty-three, a rate of prevalence of 40 per cent., of active cases of lead poisoning were found among the 402 painters examined. All of these showed definite clinical signs of plumbism; 72, or 44 per cent., of the active cases of lead poisoning among these painters were found to have lead in the urine in addition to clinical evidence. Thirty-five, or 8.7 per cent., of the total number were found to have lead in their urine without manifest clinical signs. In other words, nearly one-half of all the painters examined, or 48.7 per cent., gave evidence of active or latent lead poisoning. No attempt was made to distinguish between the effects of turpentine, benzine, wood alcohol, acetone, benzol, etc. At least 70 per cent. of all those examined gave a fairly clear and recognizable history of at least one or many attacks, and 142 painters gave a history of recent severe intoxication, in which several or even all of the following symptoms were noted: a sudden sense of weakness in the legs, irritation of the eyes, difficulty in breathing and dryness and irritation of the throat, cough, headache and dizziness, which in a number of cases was so pronounced that frequently a history of falls from scaffolding or ladders was obtained. In addition, there were often present nausea, vomiting, painful and frequent urination during the day, a few cases of bloody diarrhea, and several others of bloody urine. Practically 60 per cent. of the recent cases of turpentine and the related type of intoxications were found among our 163 active and 35 latent lead-poisoning cases out of the total of 402. Forty-seven of the 142 recent cases had suffered from frequent and moderately painful urination. Occasionally, symptoms that indicated strangury with bloody urine were described. Twenty-three of this group complained of frequent attacks of vertigo. A comparatively small number survive as active members of the trade after having attained the age of fifty years. Also, 64 per cent. of the active cases of lead poisoning occurred between the ages of thirty and forty-nine years, whereas 71, or 45 per cent., of all those who apparently were free from symptoms of plumbism were less than thirty years of age. Taken in connection with the fact that most painters enter the trade before their twentieth year, and, being skilled workers, follow it the rest of their lives, and, furthermore, that of the 109 who were more than forty years of age 59 per cent. were found to be suffering from active or latent plumbism, it seems fair to conclude that the action of lead is slow in asserting itself, but that less than half who have passed the age of forty years escape the disease. The remedial measures

that suggest themselves may be divided into two general classes: (1) public health measures, contained in better sanitary conditions for the workers, (2) and instruction in personal hygiene as applicable to the trade.

The Virulence of the Tubercle Bacilli Isolated from the Sputum.—CORPER (*Jour. Infect. Dis.*, December, 1918, No. 6, xxiii, 493) states that it is rather singular that the tubercle bacillus was one of the first pathogenic microörganisms isolated in pure culture, and yet its virulence in the sputum, the most important route of exit from the body in man, has been studied only in an unsatisfactory manner considered from a hygienic and sanitary standpoint. He isolated tubercle bacilli by Petroff's method from the sputum of 90 cases of pulmonary tuberculosis in man, of which 8 were incipient, 20 moderately advanced and 62 far advanced. The bacilli in 88 of these cases were of the human variety. Of these 88 cultures examined for virulence to guinea-pig (by subcutaneous injection), 86 proved to be virulent in amounts of 0.000,001 mg., 10 of these were not examined below this amount and 66 produced tuberculosis (beyond the local glands) in guinea-pigs within two months in 0.000,000,01 mg. amounts. One of the two low virulent tubercle bacilli only produced a slight tuberculosis in guinea-pigs in 0.001 mg. amounts within two months, while the other produced no tuberculosis beyond the local involvement even in 1 mg. amounts. No relation was observed between the virulence of the human tubercle bacilli for the guinea-pigs and rabbits and the rapidity of the disease in man. No appreciable difference, within the limits of error of the experiments, between the virulence of human tubercle bacilli tested by subcutaneous injection for young (four months) and mature (one year) male guinea-pigs was noted sixty-two days after infection. Human tubercle bacilli isolated on Petroff's medium do not appreciably alter their virulence for a period of one to three months as tested in guinea-pigs, provided no detrimental influences are introduced. A second seeding on Petroff's medium within this time produces bacilli of equal virulence to guinea-pigs to the primary. Treatment of human tubercle bacilli with 3 per cent. NaOH solution for one hour at 37° C. does not appreciably affect the virulence of the bacilli for guinea-pigs, while 6 per cent. NaOH for one hour at 37° C. will destroy the virulence of some cultures. The test for virulence of human tubercle bacilli isolated from the sputum of the same patient at different intervals (one and three months) gives concordant results in guinea-pigs.

Botulism.—DICKSON (*Arch. Int. Med.*, October, 1918, xxii, 483-495) concludes from his studies that the use of home-canned foods is not wholly unattended with danger. Various methods of canning were adopted and were followed as carefully as it is possible to have untrained persons conduct technical procedures. He states that the fact that in several instances the greater part of the home-canned material remained in good condition simply proves that though the methods are efficient in preventing ordinary spoilage, they are inefficient if the raw material happens to be contaminated with spores of B. botulinus. It is essential that only freshly picked raw material should be used for canning and it should be blanched before it is placed in jars. One outbreak showed

clearly that three hours' sterilization in the washboiler was not sufficient to kill spores of B. botulinus in vegetables which had been freshly picked and had been boiled for twenty minutes in an open kettle before being packed into 1-pint jars, a procedure which should be at least as efficient as simple blanching. Dickson further states that it is unsafe to eat or even taste home-canned products before they have been boiled. It is well known that the toxin of B. botulinus is quickly destroyed by heat. It is of the utmost importance that those who are directing the home-canning industry should recognize that the present methods of home-canning are not entirely safe, especially in the hands of untrained workers. If they will but admit this fact and will instruct the public that there is possible danger of poisoning from home-canned products, and that the danger may be averted if all home-canned food is boiled before it is eaten or even tasted, outbreaks of botulism from home-canned products will entirely cease.

Reliability of Ozone in Swimming Pool Disinfection.—MANHEIMER (*Jour. Am. Med. Assn.*, June 29, 1918, lxx, 1991–1992) recommends ozone for swimming pool purification for the following reasons: (1) It is reliable as a disinfectant; (2) it is capable of purifying heavily polluted pool water; (3) it produces no objectionable substances in the water; (4) it improves the appearance and transparency of the water, permitting a longer continued use of the pool, a consequent reduction in the cost of maintenance, and a reduction in the hazard of drowning; (5) it is inexpensive in application.

Experimental Scurvy of Guinea-pig in Relation to Diet.—COHEN and MENDEL (*Jour. Biol. Chem.*, September, 1918, xxxv, No. 3) state that experimental scurvy of guinea-pig may be demonstrated at will with suitably chosen diets. Exclusive diets of cereal grains like oats and barley produce the disease. Germinated oats or barley prevent the appearance of scurvy even when fed for comparatively long periods. Scurvy arises on a diet of soy-bean flour, even when the latter is supplemented with fat soluble and water soluble vitamines, inorganic salts and cellulose. Small additions of raw milk do not prevent the onset of scurvy. Larger quantities cause the symptoms to disappear. Roughage in the diet plays, if anything, a minor accessory role in the prevention of scurvy. This disease is not essentially dependent on constipation as a causative factor, though the latter may aggravate the symptoms. Cabbage seems to retain some antiscorbutic properties even when dried. Contrary to current statements, highly purified lactose, fed with a scurvy-producing diet appears to have no effect on the course of the disease.

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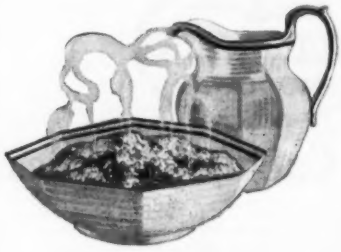

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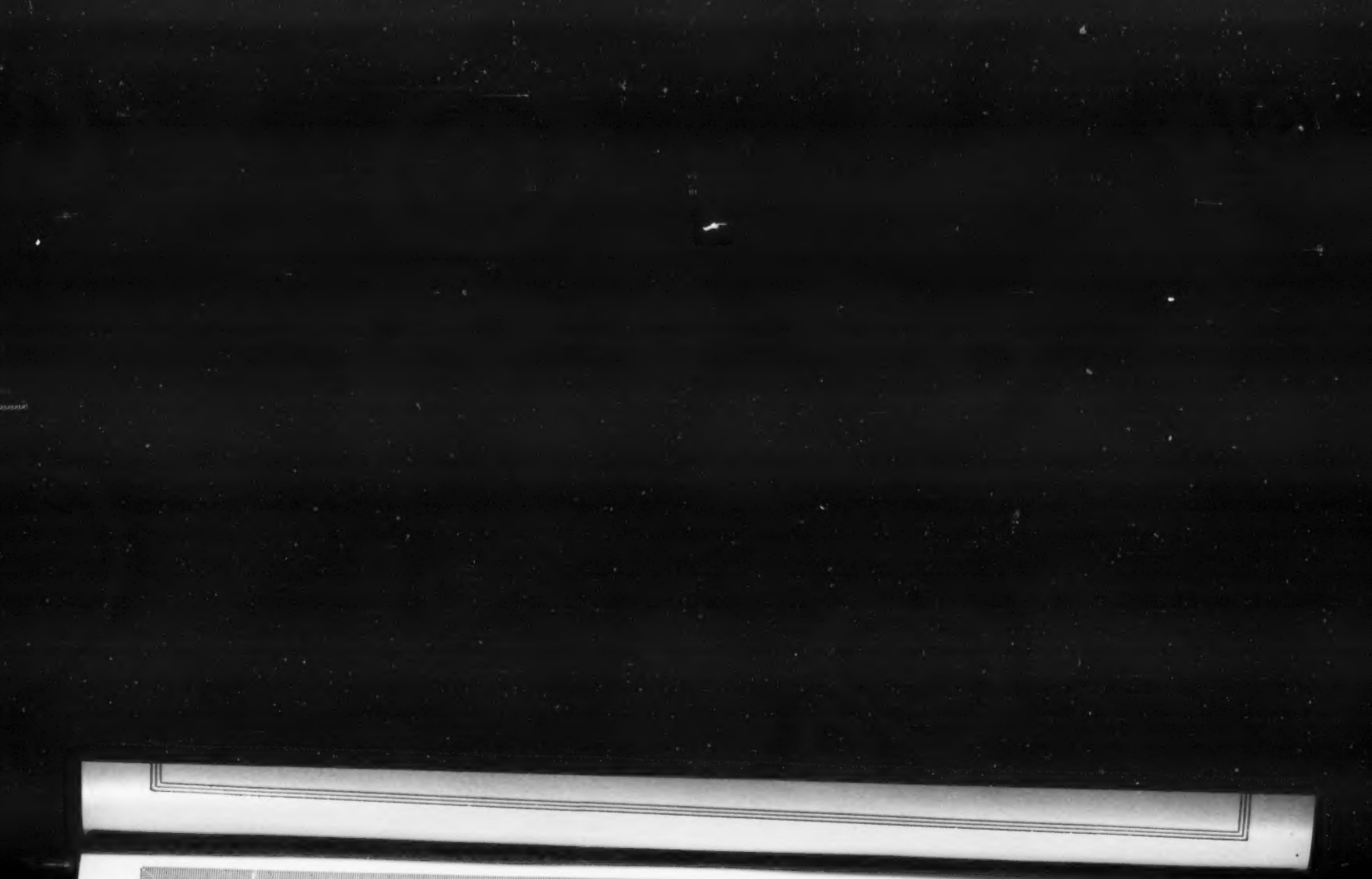

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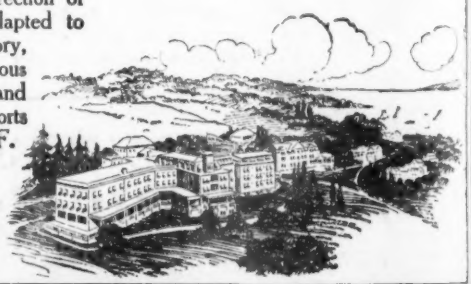

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